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A BETTER UNDERSTANDING OF UTERINE CONTRACTILITY THROUGH SIMULTANEOUS RECORDING WITH AN INTERNAL AND A SEVEN CHANNEL EXTERNAL METHOD

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A PROPER understanding of the characteristics of normal uterine contractility is necessary in order to appreciate the irregularities which exist in abnormal labors and to permit rational treatment. Uterine contractility has been studied in the past by different methods, each one of which brings into view some special aspect of the uterine function and contributes to a partial understanding of the problem. In the present work, uterine contractility is studied by the simultaneous use of two methods. This study allows integration of the results obtained by each method into a broad concept of uterine contractility and gives a much more complete and a much clearer understanding of uterine contractility than when each method is used separately.

An *external* method for recording simultaneously the activity in three separate parts of the uterus has been developed in the Department of Obstetrics of Johns Hopkins Medical School and the Department of Embryology, Carnegie Institution of Washington (7). Contractility in the fundus, in the midpart, and in the lower segment of the uterus has been recorded simultaneously. Therefore, comparison between the activity in the three parts of the uterus is possible, and experience with this method has established the concept of fundal dominance in normal labor. There is a gradient of diminishing activity from the fundus to the lower segment of the uterus, which is most often inactive (5). This method does not allow, however, exact and absolute measurement of uterine contractility, because it is influenced by a number of variable factors in different women. While this method allows comparison of the relative intensities of the contractions in the different parts of the same uterus, it is not possible to compare the intensities of the uterine contractions of different women.

An *internal* method for recording the contractility of the human uterus has been developed and used extensively in the Department of Physiological Obstetrics, Facultad de Medicina de Montevideo (1, 2, 3). The pressure which the myometrium exerts upon the amniotic fluid at any moment is recorded. This pressure is used as a measure of the intensity of the contraction of the uterus as a whole and is an exact and absolute measure of

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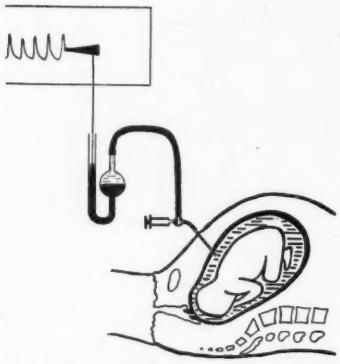

Fig. 1. Internal method used for recording and measuring the contractility of the whole uterus: the amniotic pressure is recorded with a mercury manometer.

intrauterine pressure. Therefore this method allows a comparison of the uterine contractility of different women, but it does not permit comparison of the activity in different parts of the same uterus, as does the multiple channel external method.

Therefore, the simultaneous use of both of these methods allows the exact measurement of the force and form of the contractions of the whole uterus (internal method) and the correlation of this measurement with that of the activity in the different parts of the uterus (multiple channel external method). The present report is of such a study.

METHODS

The contractility of the human uterus is recorded by the simultaneous use of the internal method and a seven channel external method.

Internal method (Fig. 1). The pressure of the amniotic fluid (which is called amniotic pressure) is recorded. With a No. 15 needle the uterus is punctured through the abdominal wall, and the amniotic cavity is reached. The needle is connected to a recording mercury manometer. The amniotic pressure is measured in millimeters of mercury. The "zero" of the scale used for this measurement corresponds to the level of the abdominal (intraperitoneal) pressure. Measured thus, the amniotic pressure corresponds to the difference existing between the pressures inside and outside the uterus, being therefore equal to the pressure exerted by the muscular walls of the uterus over its contents. We take that pressure, in each moment, as the measure of the contractile activity of the whole uterus. This procedure is harmless to the mother and fetus, as is shown in earlier papers on the subject (1, 2, 3) in which this method is described extensively.

Seven channel external method. The anterior portion of the abdominal wall over the uterus is divided into 9 areas as shown in Figure 2. These 9 areas are grouped into 3 levels, the fundus, the midpart, and the lower segment of the uterus. Each level is in turn divided into 3 areas, one along the midline or long axis of the uterus, and others to each side of it, on the right and left respectively. Seven receptors or pick-ups are used (Fig. 3). Three are strain gauges of the tokodynamometer (7). These are usually placed along the midline of the uterus, in areas *B*, *E*, and *H* (Figs. 2 and 3). In areas *A*, *C*, *D*, and *F*, 4 receptors of the uterine polygraph used by Caldeyro and Alvarez (4) are placed. These are rubber membrane pick-ups connected to sensitive frontal ink-writing Marey tambours. Each one of these 7 receptors records the local activity of the part of the uterus immediately beneath it. All have approximately the same calibration.

Recording of activity from 7 points simultaneously allows comparison of the contractility in different levels of the uterus, as in previous tokodynamometric work (5), but also the activity on the right side of the uterus may be compared with the activity on the left side.

RESULTS

Using simultaneously the internal and the external method, we recorded the uterine contractility of 18 women during labor, in the Obstetrical Clinic of the Facultad de Medicina de Montevideo. The series included normal, prolonged, and false labors. Figures 4, 5, 6, and 7 show parts of the tracings obtained in some of these cases. The small number of cases studied does not permit conclusions to be drawn on many points, such as will be possible by more extensive studies. However, several notable facts have been made clearly evident to us and these will be presented.

Fig. 2. The nine areas in which the anterior abdominal wall over the uterus is divided: *ABC*, fundus area; *DEF*, midpart; *GHI*, lower segment; *ADG*, right side; *BEH*, midline; *CFI*, left side.

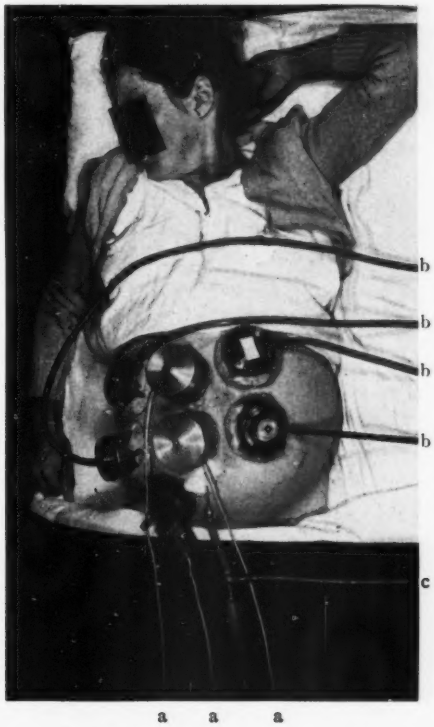

Fig. 3. Distribution of the 7 receptors of the external method. The 3 strain gauges of the tokodynamometer are placed along the midline of the uterus, in areas *B*, *E*, and *H*. They are connected by electric wires (*a*) to the tokodynamometer. The 4 receptors of the uterine polygraph are placed 2 on the right side (areas *A* and *D*), and 2 on the left side (areas *C* and *F*). They are connected to the uterine polygraph by rubber tubes (*b*). The needle inserted in the amniotic cavity communicates by means of a three way stopcock, with a syringe, and with a rubber tube (*c*) connected to the mercury manometer.

The analysis of the results is made in the following order:

1. Comparison between the activity of the different parts of the uterus.
   - A. Relative intensity of the contractions, comparison between: (a) the fundus, the midpart, and the lower segment of the uterus; and (b) the right side and the left side of the uterus.
   - B. Time relationship between: (a) the fundus, the midpart, and the lower segment of the uterus; and (b) the right side and the left side of the uterus.
2. Influence of the activity of the different parts of the uterus on the amniotic pressure.
   - A. Synchronization of activity between the different parts.
   - B Intensity of the contraction in each part.
3. The activity of the whole uterus expressed by the tracing of the amniotic pressure.
   - A. The absolute intensity of the contractions.
   - B. The regularity in the rhythm, intensity, and form of the contractions.
   - C. The descent of the amniotic pressure during the relaxation.
   - D. The frequency of the contractions.
   - E. The value of the uterine contractility in a given period of time.
4. The best characteristics of uterine contractility during labor.

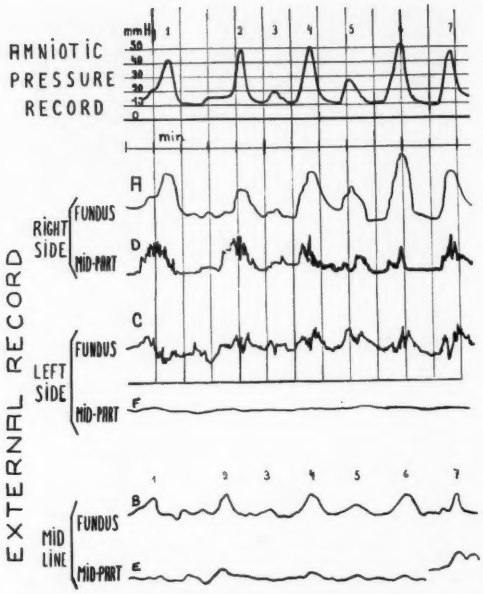

Fig. 4. Normal labor. The patient, 18 years of age, was a tertigravida, secundipara. The period of dilatation lasted 6 hours. The contractility of the uterus was recorded during a period of 2 hours. The cervix was dilated 4 centimeters at the beginning of the record, and 7 centimeters at the end of the record. Analysis of the record shows: (1) The absolute intensity of the contractions is good for labor, averaging 31 millimeters of mercury. (2) There is frank fundal dominance on the right side as shown by the fact that the relative intensity of the contractions is larger in area *A* than in area *D*. The same is true in the left side (*C*>*F*) and in the midline (*B*>*E*). The lower uterine segment is inactive and its tracing is not represented. (3) There is good synchronization between the activity of the different parts of the uterus. (4) During the relaxations the amniotic pressure descends to the level of the normal "tonus" (10 mm. Hg). (5) There is a little irregularity in the rhythm, intensity, and form of the contractions. (6) The contractions of the right side are stronger than those of the left side. The latter, being very small at first, increase progressively in intensity. (The records of the areas *F*, *B*, and *E* were made with the tokodynamometer; the other records were made with the uterine polygraph.)

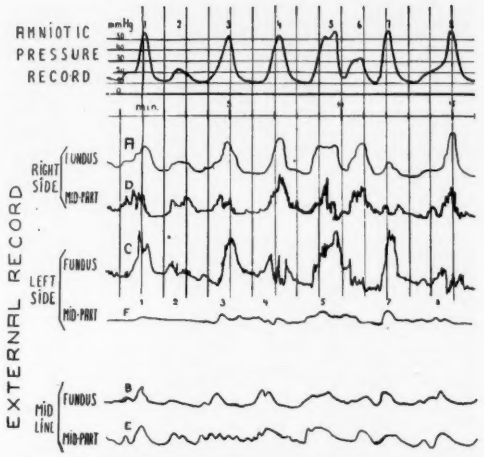

Fig. 5. Normal labor. This record is the continuation of the one shown in Figure 4. Analysis of the record shows: (1) The absolute intensity of the contractions is good for labor, averaging 38 millimeters of mercury. This value is greater than in the preceding part of the record (Fig. 4) probably because the contractions of the left side have increased very much in intensity. (2) There is good fundal dominance in the right side and in the left side, but not so evident in the midline. (3) There is good synchronization between the different parts of the uterus except in relaxation of contraction *5* (where the right side relaxes long before the left), and in contraction *6* (where the right side contracts while the left side is relaxing). (4) During the relaxation periods the amniotic pressure descends to the level of the normal "tonus" (10 mm. Hg) except in the case of contraction *5*. (5) There is some irregularity in the rhythm, intensity, and form of the contractions. (6) The right side predominates in contractions *2*, *4*, *6*, and *8*; the left side predominates in contractions *1*, *3*, *5*, and *7*. A more extensive description is given in the text. (The records of areas *F*, *B*, and *E* were made with the tokodynamometer; the other records were made with the uterine polygraph.)

THE RELATIVE INTENSITY OF THE CONTRACTIONS IN THE DIFFERENT PARTS OF THE UTERUS

Comparison between the fundus, the midparts, and the lower segment of the uterus. There is said to be fundal dominance (5) when the activity of the fundus is stronger than that of the midpart of the uterus, and there is no appreciable activity in the lower uterine segment. This distribution of intensities in uterine contractility in the different parts of the organ has been called the normal gradient of uterine contractility for labor (5). The presence or absence of fundal dominance is determined in each case by comparison of the relative intensity of the contractions between the fundus and the midpart of the uterus. This comparison is made in the right side (between areas *A* and *D*); in the left side (between areas *C* and *F*); and in the midline (between areas *B* and *E*). The lower uterine segment is generally inactive. If a receptor placed usually in area *H* verifies this inactivity, no tracing of activity in the lower segment is obtained. In the few cases in which the lower segment

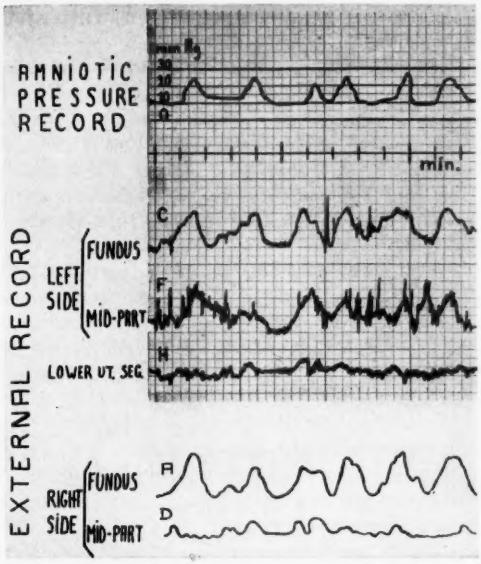

Fig. 6. Prolonged labor. The patient, 39 years of age, was a quartigravida, tertipara. There were twins. The period of cervical dilatation lasted for 16 hours. Delivery was not spontaneous, and it was necessary to employ manual extraction. The record was made during the last 3 hours of the first stage. The cervix was dilated 8 centimeters at the beginning of the record, and fully dilated at the end of the record. Analysis of the record shows: (1) The absolute intensity of the contractions is small, being about 15 millimeters of mercury on the average. (2) There is fundal dominance in the right side, but not in the left side; the lower uterine segment gives evidence of contractility, when normally it is inactive. (3) There is marked asynchronism between 3 zones of the uterus, which contract independently of each other. These 3 zones are: (a) the fundus (areas *A* and *C*); (b) area *F*; (c) areas *H* and *D*. (4) There is a marked irregularity in the rhythm, intensity, and shape of the contractions. (5) During the first relaxation, the amniotic pressure does not descend to the level of normal "tonus." This happened many times during this record. (The record of areas *A* and *D* were made with the tokodynamometer; the other records were made with the uterine polygraph.)

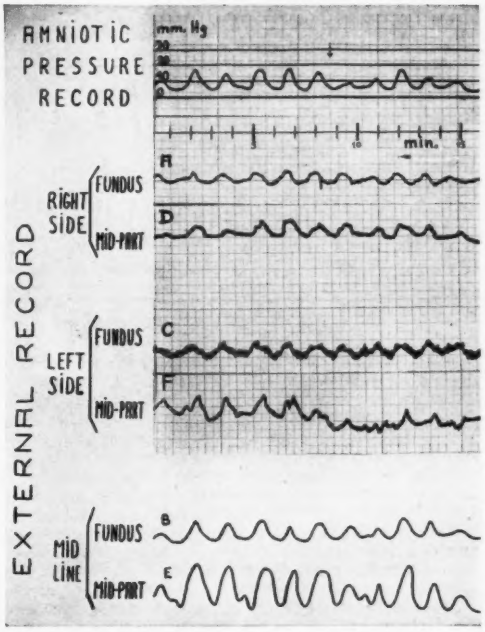

Fig. 7. False labor. The patient, 38 years old, was a tertigravida, secundipara, and had a normal pregnancy at term. For several hours before commencing the record, the woman felt contractions, and believed she was in labor. The contractility was recorded during 3 hours. At the beginning and the end of the record the cervix was in the same state: closed and not effaced. Three hours after the record, the woman felt no more contractions. Four days later, labor started spontaneously, and proceeded normally. Analysis of the record shows: (1) The absolute intensity of the contractions is very small, averaging 9 millimeters of mercury. (2) There is absence of fundal dominance, because the contractions in the midpart of the uterus (areas *D*, *E*, and *F*) have a larger relative intensity than those in the fundus (areas *A*, *B*, and *C*). (3) There is good synchronization between the different parts of the uterus. (4) During the relaxation periods, the amniotic pressure descends to the value of the normal "tonus" (this value is much less than 10 millimeters of mercury, because the woman is not in labor). (5) There is regularity in the rhythm of the contractions, but irregularity in the intensity, which increases and decreases periodically. (The record of areas *B* and *E* were made with the tokodynamometer; the other records were made with the uterine polygraph.)

exhibits some activity, its tracing is compared with those of other areas. In normal labor we find strong fundal dominance (Figs. 4 and 5). In cases of prolonged labor (Fig. 6) there is not frank fundal dominance. In the cases of false labor (Fig. 7) there is an absolute lack of fundal dominance. These results confirm the conclusions reached by Reynolds and associates (8).

Comparison between the right side and the left side of the uterus. Both sides may contract with about equal intensity (Figs. 6 and 7) or one side may contract more strongly than the other. In the case from which Figures 4 and 5 are taken, the following facts are observed. In Figure 4, the activity of the right side predominates over that of the left side; the activity of the left side is very slight at the begin-

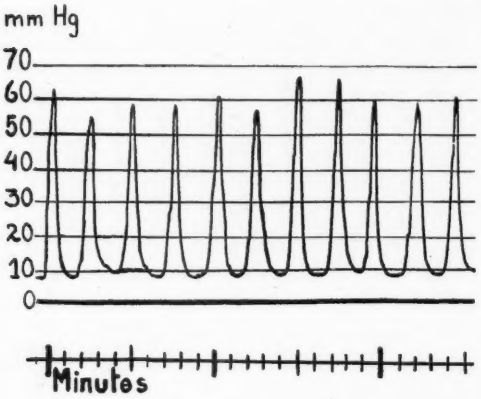

Fig. 8. Normal labor. The patient, 21 years old, was a primigravida. Labor proceeded normally and quickly. The record of the amniotic pressure shows: (1) the absolute intensity of the contractions is very large, averaging 50 millimeters of mercury; (2) there is a quite perfect regularity in the rhythm, intensity, and form of the contractions; (3) during the relaxation periods the amniotic pressure descends to the level of normal "tonus." The external records were not made because this case was studied before the internal and external methods were used simultaneously. Enlightened with the simultaneous use of both methods we can deduce that in this case there would be a very good synchronization between the different parts of the uterus, and also good fundal dominance.

ning of Figure 4, but it increases progressively. Then, in Figure 5 (which is a continuation of Fig. 4) the activity of the left side equals in intensity that of the right side. However, one may see a curious phenomenon of alternation in the predominance of the contractions between the right and the left sides respectively. The right side is predominant in contractions *2*, *4*, *6*, and *8*. The left side predominates in contractions *1*, *3*, *5*, and *7*.

At the present time we cannot draw conclusions concerning the relationship between the intensity of the contractions in the two sides of the uterus on the progress of labor. It is necessary that more extensive studies on the subject be carried out.

THE SYNCHRONIZATION OF ACTIVITY BETWEEN THE DIFFERENT PARTS OF THE UTERUS

The activity in the different parts of the uterus is normally synchronous, but it may be asynchronous. It is synchronous when all the parts of the uterus contract and relax at the same time. It is asynchronous when some parts contract while others relax.[1]

Asynchronism may exist between the right side and the left side of the uterus. In Figure 5, in the relaxation of contraction *5*, the right side relaxes while the left side remains contracted for a longer time. Then, the left side relaxes while the right side contracts, making contraction *6* in the intrauterine pressure record.

Asynchronism may also exist between the fundus, the midpart, and the lower segment of the uterus. For example, in the case from which Figure 6 is taken, there were 3 distinct rhythms in 3 parts of the uterus. These 3 parts were: (a) the fundus, (areas *A* and *C*); (b) the left side of the midpart (area *F*); (c) the lower uterine segment (area *H*) and the right side of the midpart (area *D*).

In normal labors, the majority of the contractions are synchronous, although there may be from time to time some contractions which are asynchronous. For example in the case shown in Figures 4 and 5, more than 50 contractions were recorded, and all were synchronous except the relaxation phases of contraction *5* and contraction *6*.

When there is a frank and persistent asynchronism, the progress of labor is slow. For example in the case of prolonged labor shown in Figure 6, more than 70 contractions were recorded, and most of these exhibit the asynchronism between the fundus, midpart, and lower segment of the uterus.

In the cases of false labor studied (Fig. 7) there is good synchronization between the different parts of the uterus, although there is not fundal dominance.

INFLUENCE OF THE ACTIVITY OF THE DIFFERENT PARTS OF THE UTERUS ON AMNIOTIC PRESSURE

To study this subject the tracing of the amniotic pressure is compared with the tracings simultaneously recorded by the multi-

[1]It is necessary to explain that, even in cases with good synchronization the different parts of the uterus do not begin to contract at the same moment, but with a difference of a few seconds between them. This difference corresponds to the time spent in the transmission of excitation between the different parts of the uterus. This little time difference cannot be seen in the tracings shown in this paper, because the speed of the kymograph is too slow for that purpose.

channel external method. We have found that the amniotic pressure is, in each moment, the resultant of the activity in the different parts of the uterus. The height of the elevations of the amniotic pressure caused by the contractions is determined by two factors: (a) the intensity of the contraction in each part; (b) the synchronization between the different parts.

When all the parts of the uterus contract at the same time, the amniotic pressure rises to a high value; when all the parts relax simultaneously, the amniotic pressure reaches the lowest normal value. These values occur when there is a good synchronization between the different parts, like in contractions *1*, *3*, *4*, *5*, *7*, and *8* of Figure 5. In each contraction the height attained by the amniotic pressure exceeds 50 millimeters of mercury; and during the period between contractions the pressure descends to a level of 10 millimeters of mercury, which is the value of the normal "tonus" of the uterus during labor, as explained in a previous work (3).

Between contractions *5* and *6*, the amniotic pressure does not descend to this normal value, because there is a marked asynchronism in the relaxation of contraction *5*. The right side relaxes before the left side, which remains contracted for a longer time; and when the left side relaxes, the right side is again contracting. Therefore between contractions *5* and *6* there is no moment in which all the parts of the uterus are relaxed.

In contraction *6*, only the right side contracts, while the left side is relaxing. This contraction of one side causes an elevation of the amniotic pressure that is substantially lower than when both sides of the uterus contract simultaneously. In contraction *2* the right side contracts very slightly, and the left side more slightly still. Therefore the elevation caused in the amniotic pressure is very low.

In Figure 5 the contractions cause higher elevations of the amniotic pressure than in Figure 4 (both figures belong to the same case). This difference may be explained by the fact that in Figure 5 the left side of the uterus contracts more strongly than in Figure 4.

In the case of prolonged labor, shown in Figure 6, the contractions cause low elevations

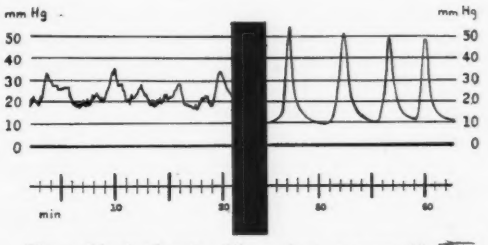

Fig. 9. Uterine inertia. The patient, 32 years old, was a primigravida. The progress of labor had stopped 12 hours before. The record of the amniotic pressure shows a very abnormal uterine contractility. A spinal anesthesia is made with percaine, up to the level of the sixth thoracic vertebra. A new record of the amniotic pressure shows that the uterine contractility has now normal characteristics. Analysis of the record shows: (A) Before the spinal anesthesia: (1) The absolute intensity of the contractions is very small, averaging 8 millimeters of mercury. (2) There is great irregularity in the rhythm, intensity, and form of the contractions. (3) The amniotic pressure never descends to the level of the normal "tonus" ("hypertonia"?). It is very possible that had the external records been made in this case, they would have shown a great asynchronism between the different parts of the uterus. (B) During the effect of the spinal anesthesia, uterine contractility has now normal characteristics: (1) The absolute intensity of the contractions is very high, averaging 40 millimeters of mercury. (2) There is great regularity in the rhythm, intensity, and form of the contractions. (3) During the relaxation periods the amniotic pressure descends to the value of the normal "tonus" (10 mm. Hg).

of the amniotic pressure (averaging 15 mm. Hg), lower than in normal labor. One of the causes of this low level must be the asynchronism between the different parts of the uterus. It is possible moreover, that each part of the uterus contracts with an intensity less than normal; but we have no means to measure exactly and absolutely the intensity of the contraction of each part.

In Figure 7, a case of false labor, the elevations of the amniotic pressure caused by the contractions, are very low (averaging 9 mm. Hg). In this case there is a very good synchronization between the different parts of the uterus. This fact would indicate that the smallness of the variation in the amniotic pressure must be due to the fact that each part contracts with very low intensity.

THE ACTIVITY OF THE WHOLE UTERUS EXPRESSED BY THE TRACING OF THE AMNIOTIC PRESSURE

According to the basis of the internal method, the amniotic pressure is, in each

moment, equal to the pressure exerted by the uterine muscle over its contents. Therefore the tracing of the amniotic pressure expresses the activity of the uterus as a whole. This is confirmed in the preceding paragraph, where it is proved that the amniotic pressure is the resultant of the activity in the different parts of the uterus.

We will review the activity of the whole uterus from five points of view.

The absolute intensity of the contractions. This is measured by the elevations of the amniotic pressure caused by the contractions. It is the most exact measure of the force exerted by the uterus to efface and dilate the cervix during the first stage of labor, and to push the fetus during the second stage. We know that the height of these elevations is determined by two factors: (a) the intensity of the contraction in each part of the uterus; (b) the synchronization between the different parts.

In normal labors (Figs. 4, 5, and 8) the average value of the intensity of the contractions is greater than 24 millimeters of mercury. In some cases it may be 50 millimeters of mercury. The values most frequently found, are between 30 and 38 millimeters of mercury. If the contractions have an intensity of less than 24 but greater than 15 millimeters of mercury, the labor may proceed, but it will be slow (Fig. 6, prolonged labor). If the intensity diminishes to less than 15 millimeters of mercury, the labor stops its progress (Fig. 9, uterine inertia). In the cases of false labor studied (Fig. 7), the intensity of the contractions is less than 15 millimeters of mercury. These small contractions are not sufficient to produce labor. These conclusions agree with the work of Alvarez and Caldeyro (3) which is based upon numerous recordings of the amniotic pressure in more than 140 patients in different stages of pregnancy and labor.

The regularity in the rhythm, intensity, and form of the contractions. The presence or absence of this regularity is very easily appreciated in the tracing of the amniotic pressure. In normal labors (Figs. 4 and 5) there is a relative regularity, which in some cases is quite perfect (Fig. 8). When disturbances in the contractility cause an abnormal labor, (Figs. 6 and 9) there is generally a great irregularity in the rhythm, intensity, and form of the contractions. The regularity in the tracing of the amniotic pressure expresses two facts: (a) regularity in the activity of each part of the uterus; (b) good synchronization between them. The alteration of either one of these two factors causes irregularities in the tracing of the amniotic pressure.

The descent of the amniotic pressure during relaxation. In normal labors (Figs. 4, 5, and 8) during periods of relaxation, the amniotic pressure descends to a level of approximately 10 millimeters of mercury. This indicates that each part of the uterus has relaxed well, and that there is good synchronization of activity between the several parts. When one of these two conditions does not occur, the descent of the amniotic pressure is not complete. This happens frequently when there are disturbances in uterine contractility (Figs. 6 and 9).

The frequency of the contractions. In normal labors the values most frequently found are between 3 and 5 contractions per 10 minutes.

The value of uterine contractility in a given period of time. In the tracing of the amniotic pressure this value is measured by the area inscribed under the elevations caused by the contractions in the same period of time (5). Roughly this value is proportional to the product of the absolute intensity and the frequency of the contractions. The relationship between the value of uterine contractility thus measured, and the duration of labor, must be more extensively investigated. We presume it to be an inverted ratio.

THE BEST CHARACTERISTICS OF UTERINE CONTRACTILITY DURING LABOR[1]

In order to produce a normal and quick labor, the best characteristics of uterine contractility, are as follows: (1) large absolute intensity of the contractions (over 24 mm. Hg); (2) strong fundal dominance; (3) good

[1]The conclusions presented are based on three kinds of investigations: (a) the studies made by Alvarez and Caldeyro with the internal method, on more than 200 women (1, 2, 3, and unpublished data); (b) the studies made with the three channel external methods by Reynolds and associates (7, 8); (c) the investigations described in the present paper, made with the simultaneous use of the internal methods and the external seven channel method. These investigations have allowed the interpretations of several facts already noticed when methods were used separately.

synchronization between the different parts of the uterus; (4) regularity in the rhythm, intensity, and form of the contractions; (5) during the periods of relaxation descent of the amniotic pressure to the level of the normal "tonus" (approximately 10 mm. Hg).

This is by no means a definitive or complete enumeration, since the influence of several other factors is still to be determined. The five factors mentioned are interrelated, and the disturbance of one of them will cause disturbances in some of the others. The two most important are absolute intensity of the contractions, and fundal dominance. When these two factors are present, labor proceeds normally (Figs. 4 and 5); when both are absent, then labor does not take place (Fig. 7). When the five factors are present the uterine contractility has been perfectly normal, and there has been a normal and quick labor. However, it remains to be established by further work just how much variation in any one or more of these characteristics there may be and still be what is called clinically a normal labor. The effect of parity, fetal position, age of the woman, and other factors on these characteristics, likewise has to be established. It is necessary also to study more abnormal labors, as well as the effect of various drugs and clinical procedures.

We have studied, with the simultaneous use of the internal and the external method, 3 cases of false labor and 3 cases of prolonged labor caused by disturbances in the contractility. The small number of cases which were studied does not permit one to draw definitive conclusions, but the facts observed are rather significant.

In the cases of prolonged labor (Fig. 6) there were the following modifications of the contractility: (a) the absolute intensity of the contractions is less than normal, varying with the cases between 15 and 24 millimeters of mercury; (b) there is not frank fundal dominance; (c) there is not good synchronism between the different contracting parts of the uterus; (d) there is irregularity in the rhythm, intensity, and form of the contractions; (e) during relaxation of contractions frequently the amniotic pressure does not descend to the level of the normal "tonus."

In the cases of false labor (Fig. 7) we found that: (a) the absolute intensity of the contractions is slight, being less than 15 millimeters of mercury; (b) there is absence of fundal dominance; (c) there is good synchronism between the different parts of the uterus; (d) there is relative regularity in the rhythm of the contractions, but irregularity in the intensity which increases and decreases by periods; (e) the amniotic pressure descends during relaxation to the level of normal "tonus."

SUMMARY

1. The contractility of the human uterus during labor is recorded simultaneously by internal and external methods. The integration of results obtained by each allows a much more complete understanding of uterine contractility than when either method is used alone.

2. The internal method consists in recording pressure variations in the amniotic fluid. This gives an exact measure of the absolute intensity of the contractions of the uterus considered as a whole.

3. The external method consists in simultaneous recording of the local activity in 7 different parts of the uterus, by means of 7 receptors, or pick-ups, applied to the abdominal wall. It is possible to compare the relative intensity and time relations of the activity in the different parts of the uterus.

4. Normally good synchronization between the different parts of the uterus is found. But sometimes an asynchronism between them is observed. For example the right side of the uterus may contract while the left side is relaxing or vice versa. The same asynchronism may be found to exist between the fundus, the midpart, and the lower segment of the uterus.

5. The amniotic pressure is, in each moment, the resultant of the activity of the different parts of the uterus. The height of the elevations of the amniotic pressure caused by the contractions is determined by two factors: (a) the intensity of the contraction in each part; (b) the synchronization between the different parts. When there is a good synchronization and all the parts contract at the same time, they cause greater elevations in the

amniotic pressure than when different parts contract at different times. The same happens in the descent of the amniotic pressure during relaxation.

6. In order to produce a normal and quick labor, the best characteristics of uterine contractility are as follows:

a. Large absolute intensity of the contractions of the whole uterus (they cause in the amniotic pressure elevations greater than 24 mm. Hg).

b. Strong fundal dominance (the relative intensity of the contractions is greater in the fundus than in the midpart of the uterus, and there is no appreciable activity in the lower uterine segment).

c. Good synchronization between the different contractile parts of the uterus.

d. Regularity in the rhythm, intensity, and form of the contractions.

e. During relaxation, the amniotic pressure descends to the level of the normal "tonus."

7. When uterine contractility deviates from these characteristics labor proceeds more slowly or it does not take place.

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BREAST ABSCESS

A Result of Lactation Failure

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THE development of a postpartum breast abscess may be best understood if it is regarded as a final stage in the failure of lactation. One of the difficulties of considering it as such stems from the fact that the care of a woman with this disease often falls between the obstetrician, the pediatrician, and the surgeon. Recent work on the let-down reflex (9, 11) makes it possible to connect infection in the breast and subsequent abscess formation with the pathological physiology of lactation as a whole.

The present study consists of an analysis of cases of breast abscess occurring in relation to pregnancy and lactation seen at the Hospital of the University of Pennsylvania from 1940 to 1949 inclusive, with a discussion of the factors involved in the development of the disease.

The study comprises in-patients at the Hospital of the University of Pennsylvania on whom a diagnosis of breast abscess was made during the years 1940 to 1949 inclusive. Only those abscesses are included which were directly connected with pregnancy and lactation. The total number of cases was 86. Of these 73 were on the obstetrical services, 12 on the general surgical service, and 1 on the gynecological service. Eighty-one occurred after delivery and 5 before. All the patients seen after January 1, 1945 received penicillin during their hospital stay, and a large number of them undoubtedly received it before they entered the hospital. Before 1945 the sulfonamides were used. The incidence of breast abscesses before and after January 1, 1945 is compared in Table I. The lower incidence in the later series probably represents the effect of penicillin on the course of the disease. The total incidence of breast abscesses in relation to delivery is similar to that found by others (6).

Thirty-eight per cent of all the cases occurred in negro women and this group accounted for 40 per cent of all the deliveries. Forty-three per cent of the patients were primiparas, and this group accounted for 42 per cent of the total births. This figure is somewhat lower than that reported by others (2, 8). The average age of the patients was 25.8 years.

Dippel and Johnston (2) found that 35 per cent of their cases occurred from January to March and 27 per cent from April to June. Table II shows that the highest incidence occurred in March, April, and May with another peak in August.

Table III shows that the onset of symptoms referable to the affected breast began during the first month after delivery in 85 per cent of the total group[1], being about evenly divided between the first and second 2 weeks. There was little difference between the results in those who were treated with and in those without penicillin.

Twenty-six per cent of the patients treated with penicillin were admitted later than the second month after delivery as compared with 12 per cent of the group not treated with penicillin. This difference is not statistically significant but suggests that the use of penicillin tended to delay abscess formation.

Twenty patients (23 per cent) gave a specific history of cracked, fissured, or bleeding nipples in the early puerperium. In all, 42 per cent of the women had some difficulty with their breasts in the first 14 days after delivery, and it is likely that the actual figure

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[1]The 5 cases which occurred before delivery have been omitted from the analysis of the history.

TABLE I.—INCIDENCE OF BREAST ABSCESSES IN RELATION TO TOTAL DELIVERIES BEFORE AND AFTER THE USE OF PENICILLIN

	Before penicillin (1940–1944)	After penicillin (1945–1949)	Total (1940–1949)
No. deliveries	5,622	8,508	14,130
No. cases of breast abscess	46	40	86
Per cent incidence of breast abscess	0.82	0.47	0.61

was higher than that since in many instances the early lactation history was not recorded on the chart.

Attempts to stop lactation do not forestall breast abscesses. In 49 women (61 per cent) a breast abscess followed by at least 7 days a definite attempt to stop lactation. This fact provides further evidence for the belief that a breast infection is not something which starts *de novo* but that it is an end result of lactation failure.

PHYSICAL FINDINGS

In most instances the typical signs of an abscess were present—localized heat, redness, tenderness, and fluctuation in the breast. In 5 cases (6 per cent) an abscess was present in both breasts either on admission or later in the course of the disease. In cases of unilateral disease the lesion was in the right breast in 42 cases (52 per cent) and in the left in 39 cases (48 per cent). There was no predominant site of abscess formation in the breast, all quadrants showing approximately the same incidence. On admission 45 per cent of the patients had a temperature of 100 degrees F. or over, and in 43 per cent the white blood count was over 12,000.

TREATMENT

In 55 cases operation was performed on the day of admission or on the next day. In 27 cases operation was deferred for several days. In 3 cases conservative treatment with chemotherapy was adopted with resolution of the abscess. In 1 case the pus was aspirated from the abscess and penicillin was injected into the cavity: the abscess resolved. The type of incision made varied with the size and appearance of the abscess and with the surgeon.

TABLE II.—ADMISSIONS BY MONTHS OF CASES OF BREAST ABSCESS (1940–1949)

	No. cases admitted	Average no. deliveries
January	6	110
February	6	107
March	10	119
April	11	109
May	13	115
June	7	120
July	6	133
August	11	125
September	1	119
October	3	121
November	7	113
December	5	124

In general, circumareolar incisions were made for superficial abscesses under or near the nipple. Radial incisions with straight drainage were used for moderate sized abscesses and multiple incisions with through-and-through drainage were made for large multiloculated lesions. The records emphasize the fact that it is important to wait until the infection is definitely localized and fluctuation is observed before operation is performed. It is frequently wiser in case of doubt to use adequate through-and-through drainage. Out of 77 cases of unilateral breast abscess treated by incision, 8 (10 per cent) required reoperation later: 2 of these needed 2 more operations. In 2 of the 5 cases of bilateral breast abscesses reincision was required.

All breast abscesses are preceded by a period of acute generalized mastitis, which usually lasts for several days. The use of penicillin in the treatment of breast infections since the beginning of 1945 is probably responsible for the subsequent lower incidence of abscess formation. However, once an abscess has developed it is questionable whether penicillin has much effect on the length or the severity of the disease. The average length of hospitalization for patients in the later group was 7.3 days as opposed to 9.0 days for those in the earlier group. This small difference may well be related to the general speeding up of hospital turnover since 1945 rather than to any specific effect of penicillin.

DISCUSSION

Three factors are usually mentioned as being important in the development of a breast abscess. These are: (1) trauma, (2) infection, and (3) stasis. Recent work on the function of the let-down reflex in human lactation (9, 11) makes it possible to clarify and co-ordinate the part played by each of these factors. The let-down reflex is a mechanism, entirely distinct from the secretion of milk, by which the mother actively expels the milk which is already in the breast in response to the stimulation of sucking. This reflex is extremely sensitive to emotional stimuli, and can be inhibited by pain, emotional upheaval, or fear (9, 16).

Inhibition of the reflex causes stasis in the breast since the milk which has already been secreted is not expelled. Recent studies at this hospital (10) suggest that early postpartum engorgement of the breast is the result in part to the fact that milk is not expelled because of poor function of the let-down reflex.

Failure of the let-down reflex may be partly responsible for injury to the nipple. If the reflex does not function properly the baby sucks without getting much milk. Gunther's studies suggest that prolonged unsuccessful sucking may produce characteristic lesions of the nipple. Injury to the nipple may in turn permit bacteria to gain access to the breast with subsequent development of infection and abscess.

It is likely that more than 23 per cent of our patients actually did have lesions of the nipple since a large number of women report nipple pain at some time during early lactation and it is difficult grossly to determine the presence or the absence of nipple fissures or cracks. Nipple injuries are extremely painful and they may in turn lead to further inhibition of the let-down reflex and the continuation of a vicious cycle.

The common infecting organism in the breast is hemolytic Staphylococcus aureus. This was found in 87 per cent of the 53 patients in whom cultures were taken. There is little doubt that the breast of every lactating mother is at some time exposed to this and other pathogenic bacteria. Entrance of bacteria into the breast must be a relatively simple matter, and it has been shown that human milk frequently does contain organisms (8). It is unlikely that any of the commonly practiced methods of nipple care keep the nipples free of bacteria, although there is some evidence that segregation of persons harboring pathogenic bacteria in the nasopharynx does diminish the incidence of infections of the breast (13).

TABLE III.—RELATION OF ONSET OF SYMPTOMS AND DATE OF ADMISSION TO HOSPITAL TO DELIVERY IN PATIENTS WITH POSTPARTUM BREAST ABSCESSES

Time after delivery	Per cent without penicillin 1940–1944	Per cent with penicillin 1945–1949	Per cent total group
Onset of Symptoms			
0–14 days inclusive	37	46	42
15–31 days inclusive	43	43	43
1–2 months	11	8	10
Over 2 months	9	3	5
Date of Admission			
0–14 days inclusive	2	8	5
15–31 days inclusive	49	34	42
1–2 months	37	32	35
Over 2 months	12	26	17

Almost all lactating women experience some trauma and some stasis of milk in the breast, and are exposed to infection. It is therefore a little surprising that more do not develop breast infections. Perhaps the explanation is that infection is the cumulative result of repeated let-down failures (with all their consequences) after lactation is well established, combined with the entrance of the infecting organism.

Emotional factors are of great importance in this sequence of events. This is well illustrated by the following case. A woman had breast fed her first 5 children without difficulty. Before the birth of her sixth child her husband died. After the baby was born "the milk just didn't seem to come down," and she developed a breast abscess.

Fulton reports an incidence of suppurative mastitis of 8.91 per cent in Dundee, Scotland, between September, 1941 and December, 1943. This period was one of grave anxiety in

Great Britain both about the war in general and bombing raids in particular, and the high rate of suppurative mastitis may well be related to these emotional factors. Fulton also noted that 16.2 per cent of those delivered in hospital developed the disease, whereas only 3.5 per cent of those who delivered at home were affected. Very few of the cases actually occurred while the patient was in the hospital. This situation may be due to the fact that the nursing mother is often exposed to more emotional stress when she arrives home after being away.

The argument against allowing lactation to continue during breast infections has been the danger of infecting the baby. None of the mothers in this series continued to lactate. It is the custom in this hospital to discontinue lactation and dry the breasts usually by means of stilbesterol when an infection does not respond very rapidly to treatment. However, in a recent series in England (17) lactation was continued on the healthy breast while milk was pumped from the affected breast, boiled, and then given to the baby. Eighty-eight women were carried through an attack of acute suppurative mastitis in this way without stopping lactation, and the babies suffered no ill effect. In addition to the advantages the baby may derive from continuing to obtain human milk, the mere fact of emptying the infected breast regularly would appear to be of value. The method necessarily requires considerable interest and supervision but has much to recommend it.

The use of stilbesterol does not necessarily prevent breast abscesses. Forty-one per cent of the postpartum patients in this series had received stilbesterol, starting in most instances at least 7 days before their admission. Stilbesterol has been used to stimulate lactation in animals (7) and Robinson has used it in the treatment of hypogalactia in women. However, it has been more commonly used to inhibit lactation. Much has been written on this subject (1). Fields, after a careful study, concluded that stilbesterol effectively aided the cessation of lactation and depressed milk secretion even in the presence of nursing, although in rare unexplained instances it was ineffective. Its exact mode of action is not known and if it is used, continued observation of the patient is necessary in case an abscess should develop.

Since the incidence of breast abscess is less than 0.1 per cent we are dealing with a relatively small proportion of the parturient population. The problem of prevention is therefore as important as that of cure. A recent study on the relation of mother's attitude to her ability to breast feed (12) shows that only mothers who wholeheartedly desire to breast feed are likely to be successful. Mothers who express indifference to or dislike of breast feeding usually secrete less milk. There is some evidence that the let-down reflex functions less adequately in these mothers, and thus they may be more likely to develop infection. If we believe that breast milk is better for the average baby (15), then we have the choice of trying to influence attitudes during period of pregnancy or of recognizing the inevitable and not allowing the mother to try to lactate. Further, it is important to help the let-down reflex function more efficiently during the early part of the puerperium. The use of drugs to relieve pain especially during nursing is particularly important. It is also essential to help mothers avoid discomfort, embarrassment, emotional disturbances, and distractions during the puerperium both in the hospital and at home.

SUMMARY AND CONCLUSIONS

1. Eighty-six cases of breast abscess occurring in relation to pregnancy and lactation in the Hospital of the University of Pennsylvania during the 10 year period 1940 through 1949 are reported.

2. The incidence of the disease has decreased from 0.82 to 0.47 per 100 deliveries since the advent of penicillin.

3. The pathological physiology of postpartum breast abscesses is discussed with emphasis placed on the belief that the disease is an end result of lactation failure in which failure of the let-down reflex plays an important part.

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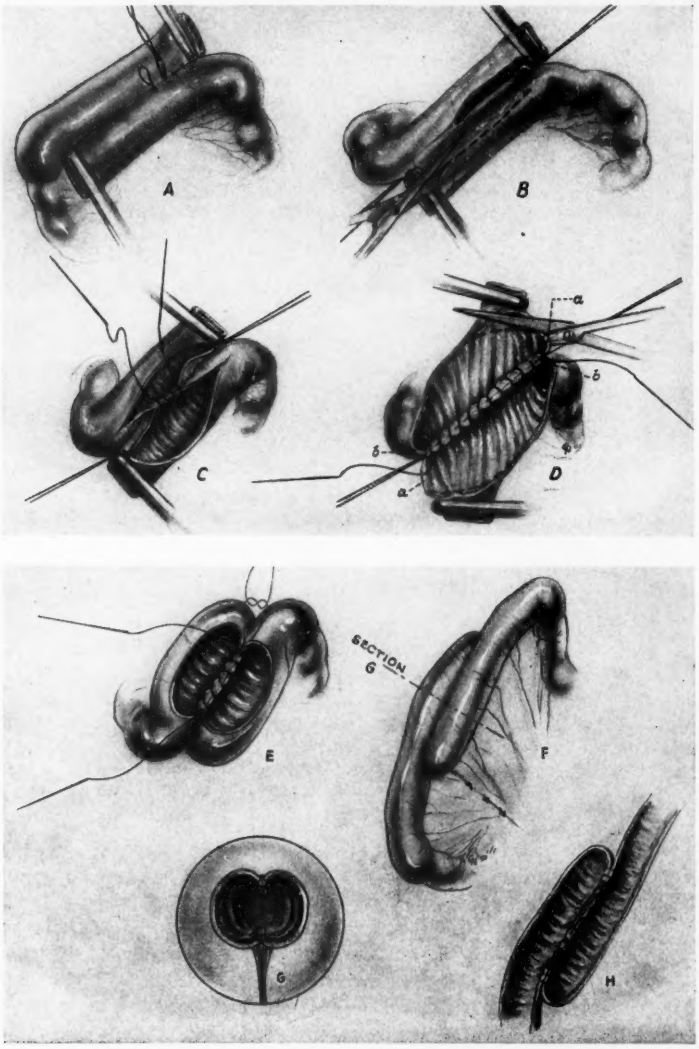

Fig. 1. A lateral-end to end-lateral anastomosis. Illustration of the suture technique applied to a side-to-side anastomosis. A, Clamps have been placed on the divided ends of the bowel which have been brought into a side-to-side position. The posterior outer row of sutures is being placed near the mesenteric border. B, The outer posterior row of sutures is complete and the loops of bowel are being incised. First a perpendicular cut is made just behind the clamp to the desired depth, scissors inserted into this opening, and then the longitudinal incision lengthened to the required extent. C, The posterior inner row is laid down. D, The excess of tissue is trimmed away. The trimmed end, *a*, is left approximately 1 centimeter longer than edge *b*, and the sutures are taken relatively further apart on this side, *a*, to gather the tissues and give a fullness which will permit placing the outer row of sutures without tension. The mesentery must be dissected back from the end about 6 millimeters. E, The anterior inner and outer rows of sutures are being placed. F, The completed anastomosis: There are no blind ends. The edges of the mesentery are closed. G, Section C. Shows the apposition of mesentery to mesentery and the extent of the stoma.

A Technique for Suturing Bowel.—Edgar J. Poth.

A TECHNIQUE FOR SUTURING BOWEL

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A NEW technique of intestinal anastomosis would seem unlikely, and so the procedure described herein may not be original. It has not been possible, however, to find this technique described. If these maneuvers are old, then they are so little known that we may well profit by redescribing them. I have frequently utilized portions of these procedures, as I am certain others likewise have, but it has been only during the past 2 years that they have been formalized and applied as definite techniques. Initially the successive steps were difficult to visualize, but now, that they are illustrated with simple drawings, little further explanation is required.

Figure 1 sets forth the basic principles of the procedure. A few technical points should be clarified. The mesentery should be cleaned from the ends of the bowel for a distance of about 5 to 6 millimeters. Cleaning the bowel for such a short distance will not impair the blood supply. In Figure 1D the end of bowel is being trimmed. It should be stressed that this edge, *a*, is left about 10 millimeters longer than the laterally incised edge, *b*, of the adjoining loop of bowel, and in placing the inner continuous row of catgut suture, somewhat longer bites are taken in the cut edge, *a*, so as to leave the fullness which is required for placing the outer suture line. A "locked" stitch should never be used.

Figure 3 illustrates a very useful application of anastomosing segments of bowel of different calibers. Figure 4 illustrates the application of this technique to the end-to-side anastomosis. When completed the segments approach each other parallel and not at right angles as occurs in the usual procedure. The cut edge of the mesentery is readily approximated to the opposite mesenteric leaf to close all defects.

The application of this technique serves to eliminate the blind ends in the side-to-side anastomosis. It affords a very desirable procedure for joining segments of loops of bowel of different calibers. It permits an essentially end-to-end suture with at least one surface of the adjoining loops being covered by serosa at all points. It provides a maximum stoma. These procedures have been applied repeat-

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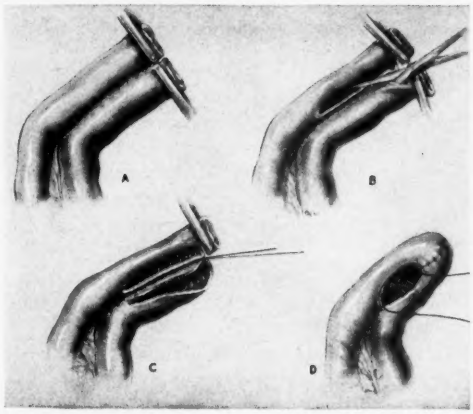

Fig. 2. Illustration of the technique applied to a blind double-ended anastomosis.

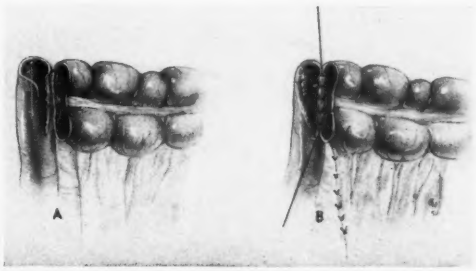

Fig. 3. Application of the technique to the anastomosis of segments of bowel of different cross-sectional areas. The end of the larger segment is sutured to the end-lateral aspect of the bowel which has a lesser caliber. The longitudinal incision of proper length is made near the mesenteric border of the lesser segment. The completion of this anastomosis is obvious. The mesenteric edges are closed. This maneuver might well be designated as a lateral-end to end suture. The use of the procedure has given excellent results both clinically and experimentally.

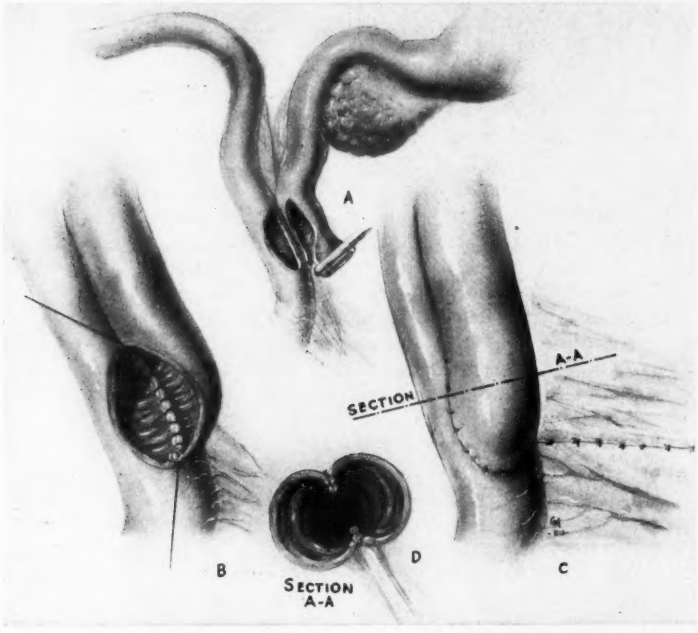

Fig. 4. The use of this technique to perform an end-to-side anastomosis is illustrated. A, The segments are brought side to side, the posterior outer row is laid down along the mesenteric border and the bowel incised to the extent desired. B, The inner suture line is being applied. C and D, Show the completed suture and the large cross-section of the stoma. This maneuver permits closure of the mesenteric edge with the two segments of bowel lying parallel to each other. This result might be called a lateral to end-lateral anastomosis.

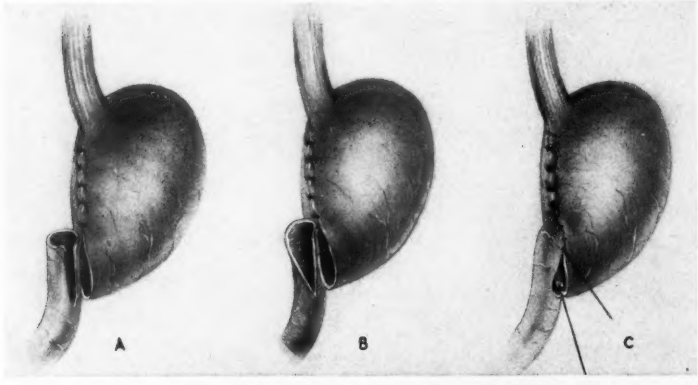

Fig. 5. Application of the suture technique to the anastomosis of the stomach to the bowel. This maneuver is particularly useful in suturing the stomach to the duodenum. The longitudinal incision in the duodenum is made on its anterior surface. The suture is applicable even when the duodenum is so short that its simple end closure is difficult. Obviously the same procedure is applicable when suturing jejunum to stomach.

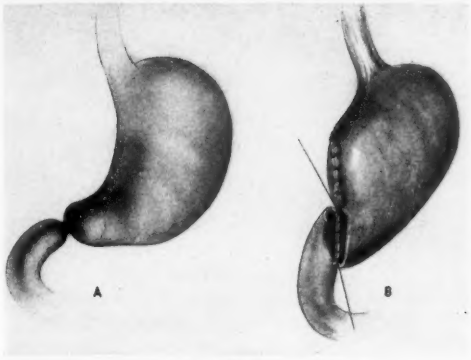

Fig. 6.

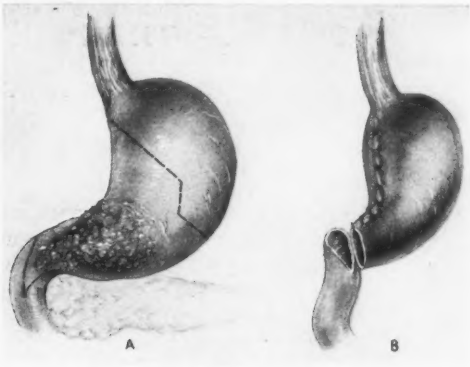

Fig. 7.

Fig. 6. Case W. F. A benign stricture at the pylorus had reduced the lumen to a diameter of approximately 5 millimeters. Although the duodenum was quite attenuated, the gastric remnant was readily anastomosed following extensive resection of the stomach. A long duodenal stump is not required.

Fig. 7. Case P. D. This carcinoma at the pyloric end of the stomach has metastasized to the liver and extended beyond the pylorus onto the anterior surface of the duodenum. After excision of the duodenal extension it was not possible to close the duodenal stump, but the gastric stoma could be brought down to serve as a pedicle and permit a very satisfactory plastic closure of the duodenum and re-establish the gastroenteric continuity. The palliative result was excellent.

Fig. 8. A demonstration of the technique illustrated in Figure 2 being applied to anastomosis of the small bowel coupled with plication of damaged loops of bowel to control the formation of adhesions and reduce the hazard of intestinal obstruction. Following completion of an anastomosis as illustrated in Figure 2, adjacent loops of bowel are plicated. The end of the anastomosis is used as the apex and starting point for the plication.

Fig. 8.

edly, both experimentally and clinically, and the results have proved to be excellent. There has been no evidence that the blood supply to the tissues is embarrassed. Microscopic examination shows unimpaired healing.

These maneuvers of necessity require that an open technique of bowel suture be employed. This limitation is not a great handicap since most intestinal anastomoses are now so executed whenever it has been possible to alter the bacterial flora of the bowel preoperatively with intestinal antiseptics. The combination of intestinal antisepsis and accurate open suture with better preservation of blood supply has wrought a significant advance in intestinal surgery.

THE PROSTATIC SMEAR

Cell Changes After Estrogen Therapy

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CYTOLOGIC changes in the prostatic secretion from patients who are receiving estrogen therapy for carcinoma of the prostate are reported in this paper. A description of the cytology of the prostatic smear has been given elsewhere (11). The usefulness of the study of exfoliated cells in the diagnosis of carcinoma of the prostate was first suggested by Mulholland and later has been studied more systematically by Herbut and others (1, 2, 4, 6, 9, 12, 14). While we were concerned with routine examination of the prostatic secretion, marked changes were observed in the cell population of the prostatic smears obtained from patients receiving estrogen therapy by mouth for carcinoma of the prostate. These cell changes were investigated and found to be characteristic. They are recorded here because they can perhaps be used as an additional guide in the hormonal treatment of carcinoma of the prostate.

METHOD

The material for cytologic examination was obtained by direct prostatic massage. A drop of the secretion was placed on a clean glass slide on which a thin film of Mayer's albumen had been spread to assure better adherence of the material. A second glass slide was then placed on top of the first one and the two pulled apart, thus preparing a thin film of prostatic secretion on both. The two slides were then submerged immediately, before the material had a chance to dry, into the fixative (equal parts of 95 per cent alcohol and ether). They remained in the fixing solution from 1 to 24 hours and were then stained with the staining procedure devised by Papanicolaou as follows:

1. The slide is rinsed successively in 70 per cent and 50 per cent alcohol and distilled water.
2. It is stained in Harris hematoxylin for 1½ minutes.
3. It is rinsed well in distilled water.
4. The slide is then placed for 1 minute in a solution of 97 cubic centimeters of 70 per cent alcohol to which has been added 3 cubic centimeters of concentrated ammonia.
5. The slide is passed through two changes of 70 per cent alcohol and then passed successively through 80 per cent and 95 per cent alcohol.
6. It is stained for 45 seconds in OG-6.
7. It is rinsed 8 times in each of two jars of 95 per cent alcohol.
8. It is stained for 1½ minutes in EA-50 multiple polychrome stain.
9. The slide is rinsed 8 times in two changes of 95 per cent alcohol.
10. It is rinsed 8 times in 100 per cent alcohol.
11. Finally, it is rinsed thoroughly in xylol and mounted.

All slides were read by one of us (H.P.).

MATERIAL AND FINDINGS

Twenty cases of carcinoma of the prostate (Cases 1 to 20, Table I) and 5 cases of benign prostatic hypertrophy (Cases 21 to 25) are presented. All patients received oral estrogen therapy; either diethylstilbesterol or ethinyl estradiol was used. Of the patients with cancer, 8 were proved pathologically to have carcinoma. Three patients had widespread metastasis as evidenced by x-ray survey and in 9 cases a clinical diagnosis of carcinoma was made. In 10 cases (Cases 1 to 10) prostatic secretion for cytologic examination was obtained for study before estrogen therapy was started. These cases showed malignant cells to be present; 1 was cytologically suspicious for malignancy (Case 1) but subsequently showed clearly malignant cells in the secretion. Three patients (Cases 11, 12, and 13) had received estrogen therapy for several

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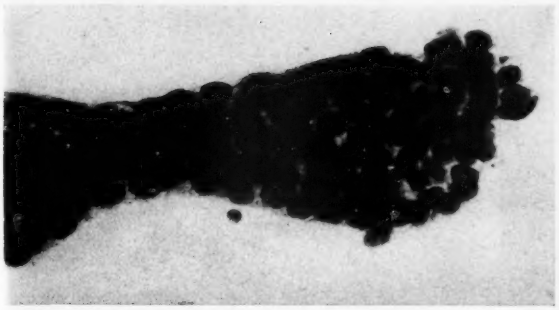

Fig. 1, left. Group of malignant cells, "cast-like" structure. ×430.

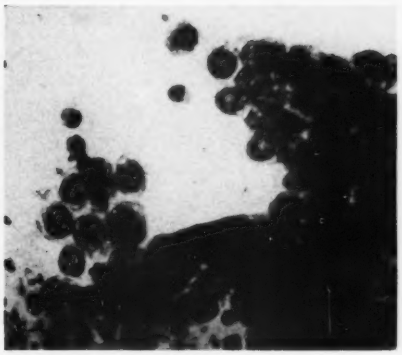

Fig. 2. Malignant cells showing chromatin patches and large nucleoli. ×430.

days, 1 week, and 2 weeks respectively before the first prostatic secretion was submitted for cytologic examination. Five patients (Cases 14 to 18) had taken estrogens 3½ to 7 months prior to the first cytologic examination. Two patients (Cases 19 and 20) had been under estrogen therapy for 1 year before their prostatic secretion was examined for the first time. In the 5 cases of clinically benign prostatic hypertrophy of the prostate the prostatic secretion was examined cytologically before estrogen therapy was started. In all cases one or more prostatic secretions were examined after estrogen therapy had been given. A detailed description of the cytologic findings and their correlation with estrogen therapy and with clinical progress is presented in Table I.

CHANGES IN MALIGNANT CELLS AFTER ESTROGEN THERAPY

Malignant cells found in secretion obtained from patients who have carcinoma of the prostate have been described previously (1, 2, 5, 11). They are usually found in dense groups, or in very large "cast-like" structures (Fig. 1). Their nuclei are large and often vary in size. They are hyperchromatic, show chromatin patches and at times large and multiple nucleoli (Fig. 2). The cytoplasm in these groups may not be visible or can be observed only at the periphery of the group. Frequently cytoplasmic vacuoles of varying sizes are seen. After estrogen therapy, changes occur in the malignant cells which may make their identification uncertain. The nuclei are still overlapping and crowded but their outline becomes irregular and indistinct. They stain uniformly dark; the chromatin detail is usually lost (Fig. 3) and their interpretation as "altered" malignant cells rests upon the appearance of the whole group. The cytoplasm is very scant or appears to be absent. Smear series examined from patients who have been under continuous estrogen therapy show the disappearance of "altered" malignant cells. Only degenerated cells and cell clumps are found. In those cases in which the clinical response to estrogen therapy was favorable, malignant cells disappeared from the smear altogether. In cases in which malignant cells

Fig. 3. Group of "altered" malignant cells; the uniformly dark staining nuclei have lost the chromatin detail. One round "glycogenic" cell in view. Several large squamous cells are seen. Patient had been taking diethylstilbesterol for 1 month. ×490.

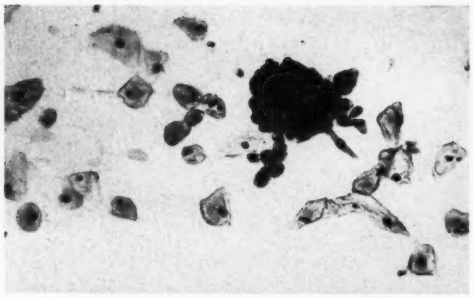

Fig. 4. "Altered" malignant cells in center of field. Many large squamous cells are seen. Smear from a patient with carcinoma of the prostate after 1 month of estrogen therapy. ×220.

persisted in the smear a failure to respond clinically to therapy was noted.

It has been reported (10) that prolonged administration of estrogens in prostatic carcinoma may cause an enlargement of the cancer cells, and thus their recognition in the the smear may be greatly facilitated. The use of estrogen therapy prior to the smear examination was therefore suggested to increase exfoliation, thus aiding in the identification of exfoliated cancer cells. We have been unable to substantiate this suggestion. A temporary increased desquamation of

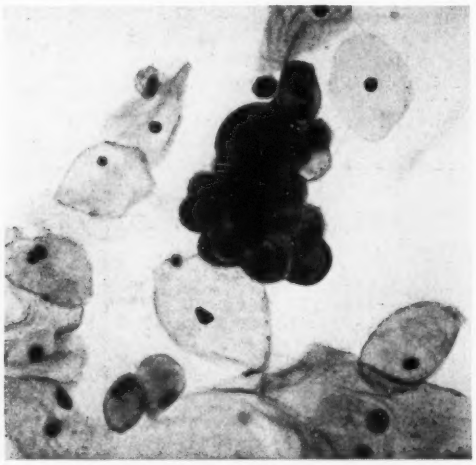

Fig. 5. Cells found in prostatic smear after 2 months of estrogen therapy. Two "glycogenic" cells are seen in left lower corner. ×430.

Fig. 6. Large group of "glycogenic" cells in prostatic smear after 10 weeks of estrogen therapy. ×220.

cancer cells after estrogen therapy was found in only 2 cases (Cases 4 and 7). Case 4 showed a remarkable increase of malignant cells in the secretion after 4 weeks of ethinyl estradiol therapy. However, smears from the same patient examined after 2 and 4 months of continued therapy failed to reveal any malignant cells in the smear. They had disappeared altogether from the prostatic secretion. In Case 7 an increased number of malignant cells was found in the smear examined after 3 weeks of continuous diethylstilbesterol therapy. This number had decreased appreciably in specimens examined 2 and 9 months later. In these 2 cases the profuse shedding of malignant cells seemed to have been a temporary effect. In none of the 18 other cases was an increase in the number of malignant cells noted after estrogen therapy.

OTHER CELL CHANGES AFTER ESTROGEN THERAPY

Squamous cells. Large polygonal superficial squamous cells are found in considerable numbers in the smears after estrogen therapy. Their cytoplasm is usually intensely acidophilic, their nucleus small and pyknotic. They desquamate in large numbers and usually constitute the majority of the cell population seen after estrogen therapy has been started. This is particularly striking in cases in which the initial smear, taken before treatment, contained none of these superficial squamous cells (Fig. 4).

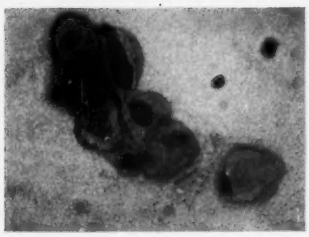

Fig. 7. "Glycogenic" cell in a prostatic smear from a patient with benign prostatic hypertrophy after he had taken diethylstilbesterol for 3 weeks. ×490.

Columnar cells. The nuclei of the columnar cells usually show some change after estrogen therapy is begun. They stain more uniformly with loss of all detail. They are not hyperchromatic but rather have a "washed out" appearance. The cytoplasm of these cells remains ample.

The "glycogenic" cell. Perhaps the most striking change in the cell population of the prostatic secretion after estrogen therapy is the appearance of a characteristic cell which is not seen before estrogen is started and which disappears shortly after estrogen therapy has been discontinued. These cells are round (Fig. 3) or oval (Fig. 5). They appear singly or in large groups (Fig. 6). On routine staining the cytoplasm appears as a thin peripheral rim, giving the cell a peculiar empty appearance. The nucleus is pyknotic, and is often displaced peripherally, thus imparting to the cell a signet ring shape. When a special stain is used (supplied by Dr. G. N. Papanicolaou), these cells are found to be filled with glycogen as described by Papanicolaou. These "glycogenic" cells appear within a few days after estrogen therapy has been started and disappear quite promptly after therapy has been discontinued. No "glycogenic" cells were found in the smear of one patient (Case 20). He took diethylstil-

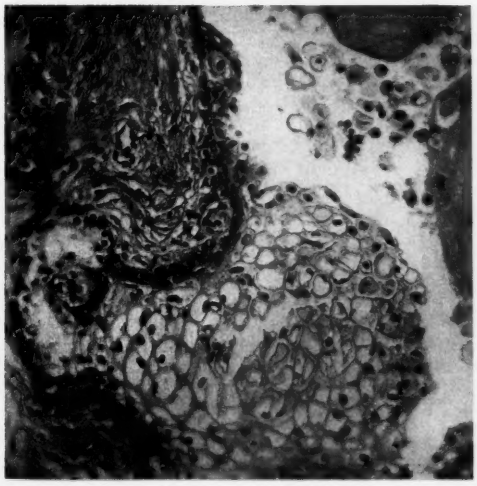

Fig. 8. Prostate, histologic section. ×215. Marked squamous cell metaplasia is seen. Patient had taken estrogens for 12 weeks. Note similarity of desquamated cells lying in lumen with those found in the prostatic secretion (Fig. 6).

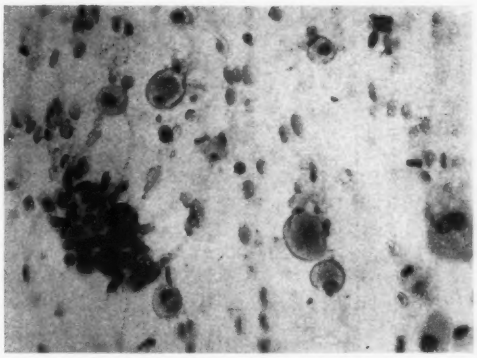

Fig. 9. Cells filled with glycogen found in a direct contact smear taken from a prostate of a newborn infant. ×300.

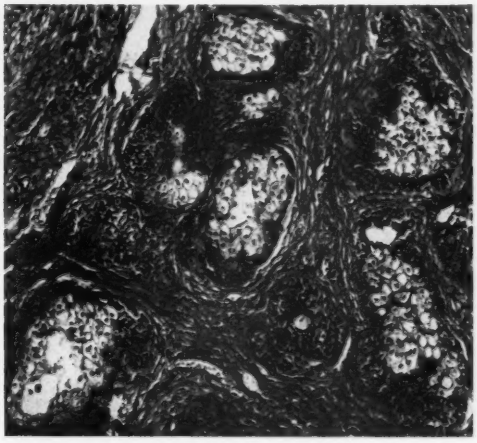

Fig. 10. Prostate, histologic section (×105) newborn infant.

TABLE I.—SUMMARY OF CLINICAL AND CYTOLOGIC FINDINGS

Case No.	Period of observation	Prostatic examination*	Clinical response†	Phosphatase King-Armstrong units	X-ray	Estrogen therapy	Operation	Cytologic interpretation	Pathology	Remarks
					Carcinoma of the Prostate					
1	Oct. '49 to Feb. '50	3° induration with extension to S.V.	Good	Oct. '49 Acid 6.6 Alkaline 35.8	Bone metastasis	10-22-49 Diethylstilbesterol 10 mgm./day continued to 2-11-50		10-22-49 Suspicious 11-12-49 3 wks. on diethylstilbesterol. Glycogenic cells 12-10-49 6 wks. on diethylstilbesterol. Malignant cells. Glycogenic cells 1-7-50 2½ mos. on diethylstilbesterol. Malignant cells. Glycogen in cells 2-11-50 3½ mos. on diethylstilbesterol. Malignant cells persist. Glycogenic cells		Cytologic and prostatic examination agree No change in size of gland Malignant cells persist during therapy
2	Dec. '49 to Feb. '50	3° induration right lobe with extension to S.V.	Poor	Normal	Negative	1-4-50 Diethylstilbesterol 10 mgm./day		12-28-49 Malignant cells in groups 2-8-50 5 wks. on diethylstilbesterol. Small malignant cells. Glycogen in cells	Biopsy Adenocarcinoma prostate	Good clinical and cytologic correlation
3	Aug. '49 to Nov. '49	3° induration right lobe	Very good	Normal	Negative	8-29-49 Ethinyl estradiol 0.05 mgm./day started	Nov. '49 Radical perineal prostatectomy	8-29-49 Malignant cells 10-17-49 6 wks. on estrogen. Degenerated (malignant) cells. Glycogenic cells 11-15-49 2½ mos. on estrogen. Glycogenic cells. No malignant cells seen	Biopsy Sept. '49 Carcinoma	Good clinical and cytologic response
4	May '49 to Feb. '50	3° induration ? of extension	Good	5-20-49 Acid 25.7 Alkaline 19.3 9-23-49 Acid 4.1 Alkaline 13.8	Feb. '50 Bone metastasis	5-20-49 Ethinyl estradiol 0.01 mgm./day 7-29-49, 0.05 mgm./day 12-5-49, 0.025 mgm./day	Nov. '49 Bilateral orchiectomy	5-20-49 Malignant cells present 6-17-49 4 wks. on ethinyl estradiol. Marked desquamation of superficial squamous and glycogenic cells. Many groups of malignant cells. 7-29-49 No malignant cells. Glycogenic and superficial squamous cells 9-24-49 Superficial squamous cells and glycogenic cells. No malignant cells seen		The clinical improvement is marked, paralleling chemical and cytologic results
5	Jan. '49 to Apr. '49	3° induration with extension	Very good	1-19-49 Acid 3.3 Alkaline 16	Negative	1-31-49 Diethylstilbesterol 10 mgm./day		1-20-49 Malignant cells present 2-28-49 4 wks. on diethylstilbesterol. Malignant cells present. Glycogenic and superficial squamous cells	1-25-49 Carcinoma	Malignant cells persist after 1 month of treatment Clinical response good after 3 months of treatment
6	Apr. '46 to Nov. '49	3° induration right lobe	Very good	1-19-49 Acid 3.3 Alkaline 16	Negative	4-30-49 Diethylstilbesterol 5 mgm./day continuous	Sept. '49 Bilateral orchiectomy	4-30-49 Malignant cells present 6-18-49 1½ mos. on diethylstilbesterol. No "fresh" malignant cells. Glycogenic and superficial squamous cells 7-8-49 2 mos. on diethylstilbesterol. Degenerating cells. Glycogenic and superficial squamous cells. 9-24-49 4 mos. on diethylstilbesterol. ? Malignant cells. Glycogenic and superficial squamous cells		Good clinical response. Acid and alkaline phosphatase values decreased at the same time as no fresh malignant cells were found in the smear. In Sept. abnormal cells found and orchiectomy done
7	Feb. '49 to Mar. '50	3° induration right lobe nodule	Poor	Normal	Question of metastasis	1948 Diethylstilbesterol 1 mgm./day 5-25-49 Diethylstilbesterol 10 mgm./day		5-18-49 Malignant cells present 6-15-49 3 wks. on diethylstilbesterol. Profuse shedding of malignant cells, profuse shedding of glycogenic and superficial squamous cells 7-27-49 2 mos. diethylstilbesterol. Malignant cells, glycogenic and superficial squamous cells 3-1-50 9 mos. on diethylstilbesterol. Malignant cells, superficial squamous cells		In this case the cytologic findings (persistent shedding of malignant cells) corroborate clinical impression of no response to therapy
8	Mar. '49 to Feb. '50	3° induration with extension left lateral lobe	Very good	Normal	Question of metastasis	3-30-49 Diethylstilbesterol 15 mgm./day 5-23-49 Ethinyl estradiol 0.05 mgm. through Dec.	January 1950 Radical perineal prostatectomy	3-23-49 Malignant cells 4-27-49 4 wks. on diethylstilbesterol. Degenerated (malignant) cells, glycogenic and superficial squamous cells 12-12-49 ? Malignant cells. Glycogen in cells	January 1950 "No definite evidence of malignancy"	

TABLE I.—SUMMARY OF CLINICAL AND CYTOLOGIC FINDINGS—Continued

TABLE I.—SUMMARY OF CLINICAL AND CYTOLOGIC FINDINGS—Continued

Case No.	Period of observation	Prostatic examination*	Clinical response†	Phosphatase King-Armstrong units	X-ray	Estrogen therapy	Operation	Cytologic interpretation	Pathology	Remarks
9	1937 to 1949	3° induration with extension to S.V. through capsule to membranous urethra	Poor Died	March '49 Acid 1.2 Alkaline 18.0	Metastasis to ilium	1943 Diethylstilbesterol 4-25-49 Diethylstilbesterol 1 mgm./day	April 1949 Bilateral orchiectomy	3-30-49 Groups of malignant cells, glycogenic cells, superficial squamous cells		Despite many years of estrogen therapy malignant cells are shed. Patient died September 1949
10	Nov. '48 to Jan. '50	3° induration with extension to left S.V.	Poor	Nov. '49 Alkaline 16.1	Negative	8-5-49 Diethylstilbesterol 10 mgm./day		March '49 Malignant cells 8-19-49 2 wks. on diethylstilbesterol. Glycogenic cells, no malignant cells		
11	Jan. '49 to Jan. '50	3° induration with extension to right S.V.	Very good			Diethylstilbesterol therapy Spring '49 to July '49 Started again 1-2-50	1-7-50 Bilateral orchiectomy 1-12-50 Transurethral resection	1-6-50 4 days after unknown dose of diethylstilbesterol was started; malignant cells present, superficial squamous cells No glycogen in cells 2-20-50 7 wks. after estrogen therapy started. Degenerated cells		No glycogenic cells found
12	July '49 to Jan. '50	3° induration with extension to S.V.	Good	Normal	Negative	7-19-49 Diethylstilbesterol 5 mgm./day 8-2-49 Diethylstilbesterol 15 mgm./day		7-26-49 1 wk. on diethylstilbesterol. Malignant cells, *no* glycogenic cells 8-2-49 2 wks. on diethylstilbesterol. Malignant cells, glycogenic cells 9-13-49 2 mo. on diethylstilbesterol. No "fresh" malignant cells (smudged cells). Glycogen in cells 1-3-50 Has been off diethylstilbesterol for several days. Malignant cells present		Malignant cells reappear after diethylstilbesterol is omitted
13	Oct. '49 to Feb. '50	3° induration with extension to both S.V.	Very good	Oct. '49 Alkaline 15 Acid 5 Feb. '50 Alkaline 2.1 Bodanski Acid 1.5	Pelvic metastasis	10-18-49 Diethylstilbesterol 10 mgm./day In Dec. intermittent, stopped in Jan.		11-1-49 2 wks. on diethylstilbesterol. Atypical cells (suspicious), glycogenic cells 11-14-49 4 wks. on diethylstilbesterol. Malignant cells in groups. Glycogenic and superficial squamous cells 1-12-50 No malignant cells, no glycogenic cells		Good clinical response and disappearance of malignant cells
14	1937 to 1-18-50	3° induration left lobe with extension to S.V.	Good	1944 Normal Sept. '49 Alkaline 21.7	Negative	Sept. '43 to Feb. '45 Took diethylstilbesterol. Started again on 9-30-49 5 mgm./day continued through Jan. '50	Jan. '49 Bilateral orchiectomy	1-18-50 On diethylstilbesterol 3½ mos. Malignant cells and glycogen filled cells	6 biopsies 1 shows carcinoma	Continues to shed malignant cells while on therapy. Clinical response good
15	Sept. '46 to Jan. '50	3° induration right lobe	Good	Normal		Diethylstilbesterol therapy started Apr. '47 off and on Dec. '48 5 mgm./day continuous to Jan. '50		3-24-49 Continuous diethylstilbesterol for 4 mos. Small groups of malignant cells (altered by diethylstilbesterol) glycogenic cells June '49 6 mos. continuous diethylstilbesterol. Glycogenic and superficial squamous cells, no malignant cells	April 48 Question of carcinoma	Good clinical response and disappearance of malignant cells after 6 months of continuous therapy
16	Oct. '49 to Jan. '50	3° induration with extension to S.V.	Very good	Normal	Negative	May 49 Unknown doses of estrogen and testosterone 12-19-49 Ethinyl estradiol 0.05 mgm.		10-12-49 On estrogen and testosterone for 5 mos. "Washed out" malignant cells 12-9-49 No estrogen for 2 mos. Many large groups malignant cells 1-16-50 On ethinyl estradiol 4 wks. Malignant cells present. Glycogenic and superficial squamous cells	Dec. '49 Biopsy carcinoma 2 previous biopsies negative	Very good clinical response to therapy but malignant cells persist

TABLE I.—SUMMARY OF CLINICAL AND CYTOLOGIC FINDINGS—Continued

Case No.	Period of observation	Prostatic examination*	Clinical response†	Phosphatase King-Armstrong units	X-ray	Estrogen therapy	Operation	Cytologic interpretation	Pathology	Remarks
17	Jan. '48 to July '49	3° induration right lobe with extension to S.V.	Poor	Normal		Diethylstilbesterol 5 mgm./day Sept. '48 to May '49. Started again July '49	2-28-48 Transurethral resection	3-11-49 On diethylstilbesterol for 6 mos. Profuse desquamation of superficial squamous cells, glycogenic cells and "altered" malignant cells	Feb. '48 Benign prostatic hypertrophy	
18	Jan. '49 to Nov. '49	3° induration with extension beyond capsule on both sides	Good	Normal		Diethylstilbesterol 5 mgm./day started in Nov. '48 8-29-49 Ethinyl estradiol 0.02 mgm.	Nov. '49 Bilateral orchiectomy	6-20-49 7 mo. on diethylstilbesterol. Profuse desquamation of glycogenic cells 11-7-49 2½ mos. on ethinyl estradiol. An occasional atypical cell		No malignant cells found in initial slide which was taken several months after diethylstilbesterol was started
19	Aug. '48 to Jan. '50	3° induration right lobe with extension to S.V.	Poor	Normal	Negative	Aug. '48 Diethylstilbesterol 25 mgm. tid. Jan. '49 Ethinyl estradiol .05 mgm. continuous		9-9-49 1 yr. diethylstilbesterol. Degenerated (?malignant) cells. Glycogenic cells 1-13-50 Degenerated cells		
20	March '48 to May '49	3° induration with extension to S.V.	Poor	Normal	Negative	March '48 Diethylstilbesterol 5 mgm./day off and on Jan. '49 Every other day	July '49 Bilateral orchiectomy	May '49 1 yr. diethylstilbesterol Malignant cells in large sheets		Diethylstilbesterol is taken off and on. No glycogenic cells seen
Benign Prostatic Hypertrophy										
21	11-3-49 to 1-3-50					11-14-49 Diethylstilbesterol 5 mgm./day 12-13-49 D.C.		11-3-49 Small columnar cells 11-29-49 2 wks. after diethylstilbesterol. Glycogenic cells Jan. '50 3 wks. after discontinuance of diethylstilbesterol. No glycogenic cells		Glycogenic cells appear after stilbesterol therapy, disappear after therapy has been discontinued
22	Nov. '49 to Mar. '50					11-22-49 Diethylstilbesterol 5 mgm./day 12-22-49 D.C.		11-29-49 1 wk. on diethylstilbesterol. Glycogen in cells 12-27-49 5 wks. on diethylstilbesterol. Glycogenic cells, smudging of nuclei of columnar cells 3-7-50 No glycogenic cells		Glycogenic cells appeared 1 wk. after diethylstilbesterol was started
23	12-13-49 to 1-10-50					12-13-49 Diethylstilbesterol 10 mgm./day		12-13-49 Single columnar cells 12-27-49 2 wks. on diethylstilbesterol. Glycogenic cells		Breasts got sore and patient probably did not take tablets. No change in cytology after 2 wks. on diethylstilbesterol
24	1943 to 1949					8-16-49 Diethylstilbesterol 10 mgm./day		8-16-49 Single columnar cells 8-22-49 1 wk. on diethylstilbesterol. Glycogenic cells		Glycogenic cells appear in 1 wk. after diethylstilbesterol therapy
25	Aug. '49 to Jan. '50					8-23-49 Diethylstilbesterol 10 mgm./day 9-10-49 Diethylstilbesterol discontinued methyltestosterone started 9-27-49 Methyltestosterone discontinued diethylstilbesterol 10 mgm./day 12-8-49 Discontinued		8-8-49 Single columnar cells 8-30-49 1 wk. on diethylstilbesterol. More columnar cells, glycogenic cells 9-27-49 2 wks. on testosterone. Single prostatic cells, no glycogenic cells 10-25-49 3 wks. on diethylstilbesterol. Glycogenic cells 1-12-50 No diethylstilbesterol for 4 wks. No glycogenic cells		Glycogenic cells appear when diethylstilbesterol is taken, disappear when it is discontinued

*3° induration indicates a stony hard gland which is generally accepted as characteristic of carcinoma of the prostate.
S.V. abbreviation for seminal vesicles.
†Poor indicates essentially no change in consistency and size. Very good indicates marked reduction in size and hardness of the prostate. Good indicates softening of the prostate but little change in size of the gland.

besterol intermittently and had taken none for several days before the smear was prepared. Of the 20 patients with carcinoma of the prostate who were taking estrogens continuously, 1 failed to show "glycogenic" cells in the prostatic smear (Case 11). Orchiectomy had been performed on him at the same time hormone therapy was started. We have no explanation for the failure of the "glycogenic" cells to appear in this case.

The "glycogenic" cell does not only appear in the smear of patients who have carcinoma of the prostate but also in those who are free of the disease after estrogens have been taken by mouth (Fig. 7). Five patients who had benign prostatic hypertrophy were given diethylstilbesterol for 1 to 4 weeks. All but 1 showed the appearance of "glycogenic" cells in the prostatic secretion. The patient whose smear did not contain "glycogenic" cells reported soreness of his breasts, and there is some indication that he failed to take the medication for 1 or 2 days before returning to the clinic. Perhaps the presence or absence of the "glycogenic" cell in the smear can be used to indicate whether or not estrogen medication has been taken by the patient.

The question arose as to whether the "glycogenic" cells come from the prostate itself. Direct smears prepared from prostates removed by surgery from patients who had received estrogen therapy for carcinoma showed the glycogen-containing cell. The histologic sections showed marked metaplasia of cells lining acini (Fig. 8). Desquamated cells in the lumen of acini were of same shape and form as those seen in expressed secretion.

We became interested to learn whether the "glycogenic" cell could be found in other conditions in which the estrogen blood level is high in the male. This occurs physiologically late during fetal life (15). Direct smears were prepared from prostates of 7 month old fetuses as well as from those of newborn full term infants. Characteristic cells filled with glycogen were found in these contact smears (Fig. 9). Histologic section of these prostates (Fig. 10) also showed marked metaplasia (3) and the lumina of the acini were filled with characteristic cells which Schlachta described in 1904 as containing glycogen.

TABLE II.—CORRELATION BETWEEN CLINICAL RESPONSE AND CYTOLOGIC FINDINGS

Clinical response to estrogen therapy	Cytologic agreement	Cytologic disagreement
Good	8	3
Poor	7	0
Total	15	3

DISCUSSION

That carcinoma of the prostate will regress and remain latent for some time under estrogen therapy has been well established by the work of Huggins and others. Schenken, Burns, and Kahle demonstrated the cellular changes induced by diethylstilbesterol in carcinoma of the prostate as seen in histologic sections. They described neoplastic cells which after estrogen therapy showed definite nuclear and cytoplasmic regression. These progressive degenerative changes can be observed in the desquamated cell as seen in the prostatic secretion. The correlation between the clinical response to estrogen therapy and the cytologic findings has been encouraging in our limited experience. Of the 18 cases so correlated (Table II), 8 patients responded well to estrogen therapy. Their prostates decreased in size and changed from a stony hard induration to the softer consistency as found in benign prostatic hypertrophy. The prostatic smear in these cases showed either appearance of characteristic degenerated cells after hormone therapy had been started, or if the period of observation was long enough, a final disappearance of malignant cells from the smear. In 3 cases in which the clinical response to therapy was good, malignant cells continued to be shed into the prostatic secretion. The time of observation has as yet been too short to learn the clinical significance of the persistent shedding of cancer cells. In 7 cases clinical response to estrogen therapy was considered to be poor. The prostate showed no change in consistency and size. Cancer cells persisted unaltered in the smear of these patients which suggested a failure of the prostatic cancer tissue to respond to hormone therapy.

Though the group of patients presented is small, the results suggest that the prostatic

S.V. abbreviation for seminal vesicles, gland which is generally accepted as characteristic of carcinoma.
Very good indicates marked reduction in size and hardness of the prostate.
Good indicates softening of the prostate but little change in size of the gland.
†Poor indicates essentially no change in consistency and size.

smear can be used as an additional objective means of following the response of carcinoma of the prostate to hormonal therapy.

SUMMARY

1. Cell changes have been described which occur in the prostatic smear after estrogen therapy.

2. A correlation of the clinical response to estrogen therapy and of the cytologic findings in the prostatic smear was made in 18 cases of carcinoma of the prostate.

3. It is suggested that the cell changes in the prostatic smear can be used as an additional guide in the hormonal treatment of carcinoma of the prostate.

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STUDIES ON THE SUSCEPTIBILITY OF BACTERIA TO VARIOUS ANTIBACTERIAL AGENTS WITH A COMPARISON OF THE SERIAL TUBE DILUTION AND FILTER PAPER DISC METHODS OF TESTING

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VARIOUS authors have described methods for determining the drug susceptibility of bacteria. Rammelkamp's serial tube dilution technique is widely used and is particularly adaptable to testing single strains of organisms (12). Pulaski has described a similar method employing a four tube setup. Vincent and Vincent, Bondi, Meleney, and others have described filter paper disc, blood agar plate techniques for testing the sensitivity of bacteria to antibacterial agents. The latter method is more rapid and appears preferable to tube dilution techniques for testing the polymicrobial flora commonly seen in surgical infections (2, 3). Hence it became desirable to determine how these methods compared in accuracy.

Observations on the sensitivity to various antibacterial agents were made on a group of 50 organisms. Ten strains each of Staphylococcus aureus, hemolytic streptococcus, Pseudomonas aeruginosa, and Proteus vulgaris were tested by the serial tube dilution technique using a 24 hour broth inoculum diluted 10^{-6}, and compared with the sensitivities obtained using a quantitative paper disc method with the same inoculum. This afforded opportunity to compare the two methods of testing and to evaluate the relative efficiency in vitro of the various antibacterial agents studied.

MATERIALS AND METHODS

The 50 strains of organisms were isolated from surgical infections encountered on the wards of the Massachusetts Memorial Hospitals and were tested for drug susceptibility against those available antibacterial agents which seemed most likely to be effective against each particular group of organisms. Serial dilution tests were performed according to the method diagrammatically illustrated in Figure 1. The filter paper tests were carried out as follows: Four paper discs wet with graded dilutions of drug and a normal saline control were placed on a single freshly inoculated, dried, blood agar plate for 10 minutes, and the readings were taken after overnight incubation at 37 degrees C. (Fig. 2). The inoculum consisted of 0.25 cubic centimeter of a 24 hour broth culture diluted 10^{-6}. Various antibacterial agents differ in their rate of diffusability through agar. Therefore cultures were examined only for the presence or absence of bacterial growth over the area of disc contact. No attention was given to the width of diffusion zones.

Sensitivities were plotted as columns rising from a baseline, each block representing one strain of the organism and each column representing the antibacterial agent tested (Figs. 3 to 7). The shaded columns represent serial dilution tests and the unshaded ones the paper disc method. Extreme variations in drug sensitivity ranges necessitated the use of a semilogarithmic type of scale which expresses units, per cent or gamma as the case may be. It must be remembered in interpreting the charts that these various denominations are not comparable. The shortest columns represent the most sensitive organisms, the longest the most resistant. A plus sign over a column indicates that the level of sensitivity was at a concentration greater than tested; a minus sign indicates the possibility that the organism is sus-

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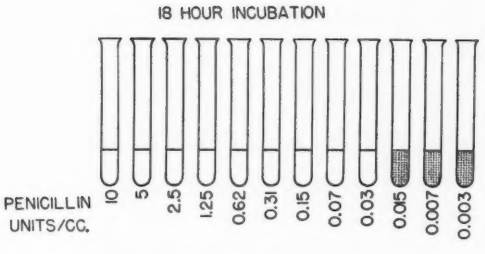

Fig. 1. Diagrammatic illustration of the type of serial tube dilution sensitivity test used in this study. Broth dilutions of Staphylococcus aureus were made according to the technique of Rammelkamp. The inoculum consisted of 0.5 cubic centimeter of a 24 hour broth diluted 10^{-6}.

ceptible to a concentration less than indicated inasmuch as the highest dilution tested was bactericidal. Several blood agar plates were used if necessary to span the indicated ranges.

RESULTS

Sensitivity levels are recorded graphically in Figures 3 to 7. It can be seen that the unshaded columns are uniformly higher than the shaded ones indicating that the paper disc method consistently gives more resistant readings than the tube dilution technique (i.e. paper disc sensitivity readings are several serial dilutions lower). There appears to be a fairly constant rough relationship between results obtained with the two methods especially in the clinically effective concentrations. Information regarding the effectiveness of the various antibacterial agents and the variations in sensitivity of different strains of the same organism can be obtained by reference to the figures as it is more readily imparted by the charts than by lengthy textual description.

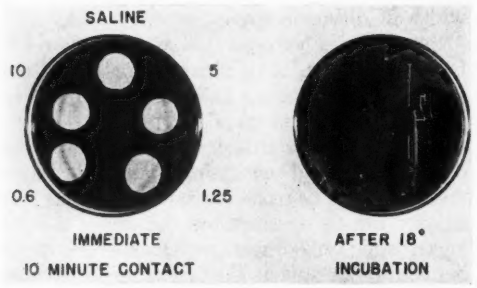

Fig. 2. Illustration of the modification of the filter paper disc method of sensitivity testing used to compare with the serial tube dilution technique. The inoculum consisted of a 24 hour broth culture diluted 10^{-6}. Numbers around the left hand blood agar plate indicate the concentration of penicillin in units per cubic centimeter used to wet the respective discs before application to the plate. This strain of Staphylococcus aureus was sensitive to 1.25 units of penicillin per cubic centimeter but resistant to 0.6 unit per cubic centimeter.

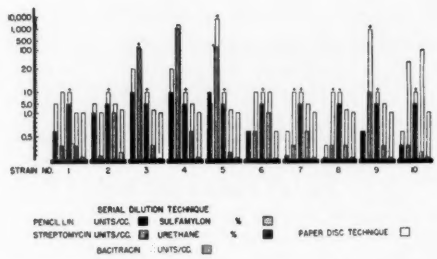

Fig. 3. Sensitivity tests on 10 strains of Staphylococcus aureus.

COMMENT

Staphylococcus aureus (*Fig. 3*). The variation in sensitivity to penicillin is apparent. It will be noted that strains 3, 4, and 5 are resistant to penicillin and relatively sensitive to bacitracin. The sensitivity to streptomycin is also variable but most strains are susceptible to less than 25 units per cubic centimeter. In my experience in vitro drug susceptibility testing of urethane has not been a sensitive indication of its clinical effectiveness. Five per cent urethane was bactericidal for all strains by the tube dilution technique. Urethane tests were not carried out above 10 per cent by the disc method because it is felt unsafe to use higher concentrations in the treatment of patients due to its absorption through tissues and the danger of leucopenia.

Sulfamylon was the most uniformly effective drug tested against the staphylococci, all 10 strains being sensitive to 0.015 per cent or less in vitro by the tube dilution method and 2.5 per cent or less by the disc technique.

There seemed no relationship between drug susceptibility and coagulase test. Strains 1, 4, 5, 6, 7, and 8 were coagulase positive while 1, 3, 9, and 10 were coagulase negative.

Streptococci (*Fig. 4*). The 10 strains of hemolytic streptococci were uniformly sensitive to

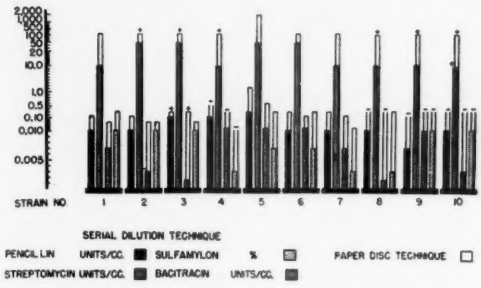

Fig. 4. Sensitivity tests on 10 strains of streptococcus.

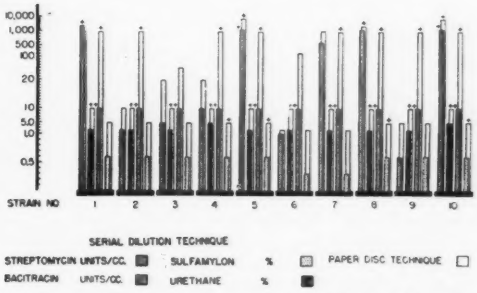

Fig. 5. Sensitivity tests on 10 strains of Escherichia coli.

penicillin, bacitracin, and sulfamylon and there was less variation in individual strain sensitivity than with Staphylococcus aureus. Strains 2, 3, 5, 6, and probably strain 10 are resistant to streptomycin while the remaining organisms were killed by 10 units per cubic centimeter of this drug. None of the streptococci exhibited a degree of sensitivity to streptomycin comparable to that of the staphylococcus group.

Escherichia coli (*Fig. 5*). The extreme variation in sensitivity to streptomycin is noteworthy. Strains 1, 5, 7, 8, and 10 are very resistant to it while the others are not. Serial tube dilution tests were not carried out above 10 units per cubic centimeter of bacitracin and all strains were resistant to this amount of the drug. Bacitracin disc sensitivity tests were carried out at greater concentrations and all strains proved resistant to above 1,000 units per cubic centimeter except 2 (strains 3 and 6). Figure 5 demonstrates a high degree of susceptibility to sulfamylon, all strains being sensitive to a concentration of 0.6 per cent or less by the serial tube dilution technique and 2.5 per cent or less by the paper disc method.

Proteus vulgaris (*Fig. 6*). The variation in susceptibility to streptomycin is apparent, half of the strains being resistant and the remainder sensitive. The same uniformity of sensitivity levels to urethane is demonstrated for this organism by both methods. All strains were bacitracin resistant and quite susceptible to sulfamylon.

Pseudomonas aeruginosa (*Fig. 7*). Strains 1, 3, 5, and 9 are sensitive to streptomycin, the others being resistant. The same meaningless uniformity of urethane susceptibility levels and the same resistance to bacitracin are demonstrated as were shown for the other gram negative organisms. Pseudomonas aeruginosa appeared extremely susceptible to sulfamylon with sensitivity readings varying from 0.007 to 1.25 per cent by tube method and 0.6 to 1.25 per cent by disc technique.

The data reported here emphasize the variation in sensitivity of different strains of the same organism to an antibiotic. This is es-

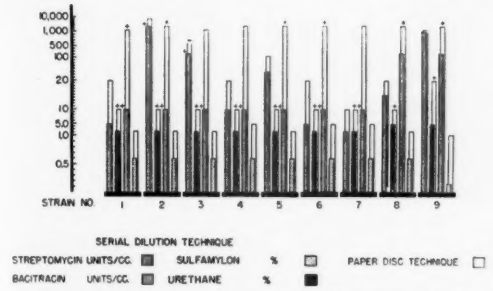

Fig. 6. Sensitivity tests on 9 strains of Proteus vulgaris.

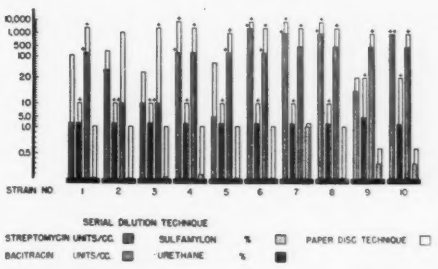

Fig. 7. Sensitivity tests on 10 strains of Pseudomonas aeruginosa.

pecially true for penicillin and streptomycin in all groups except the hemolytic streptococci and points to the desirability of treatment based on in vitro drug susceptibility testing if one is to avoid the indiscriminate waste of antibiotics.

Sensitivity tests were carried out on urethane for all organisms because we have been studying the effect of the carbamates on bacteria. Urethane has been useful in preparing constantly contaminated wounds for secondary closure (5) and is particularly effective against certain gram negative organisms (6). It must be used with caution because it is absorbed through tissues and can cause severe leucopenia. Although we have used it in the treatment of over 100 surgical infections without this complication, agranulocytosis resulting in death has been reported after using urethane over large burned areas in a 19 month old baby (4, 10). It is a valuable antibacterial agent for certain gram negative infections which are resistant to other drugs and its use should be limited to small wounds and controlled by daily white blood counts. Treatment should be omitted if the white count falls below 5,000 per cubic millimeter (13). In vitro testing for urethane has been unsatisfactory in that fine gradations of susceptibility levels are not obtained by the methods described and the sensitivity tests do not seem to indicate its clinical effectiveness. The most sensitive organism yet tested in vitro was killed by 1.25 per cent urethane. This drug leaves wounds particularly bright, clean, and soft.

The sensitivity levels recorded here for sulfamylon indicate that it is perhaps the most useful drug for topical therapy of those tested. All organisms were susceptible to levels well below the concentration commonly used for clinical application. Sulfamylon in 5 per cent solution and streptomycin 200 units per cubic centimeter have been advocated by Howes (7, 8) for topical therapy in the prevention of wound infection. Our own experience with this combination in the treatment and prevention of wound sepsis has been extremely satisfactory. Drug susceptibility testing has indicated it to be the combination of choice in the majority of instances and consequently we have used it with increasing frequency.

SUMMARY AND CONCLUSIONS

Comparative studies indicate that the drug susceptibility levels of bacteria tested by the filter paper disc contact method are usually several serial dilutions lower (more resistant) than levels obtained by the tube dilution technique. There appears to be a fairly constant rough relationship between the two methods.

The variation in drug susceptibility of different strains of the same organism is again demonstrated and the need for the appropriate choice of antibacterial therapy based on in vitro testing is emphasized.

Attention is called to the marked in vitro susceptibility to sulfamylon of certain gram positive and gram negative bacteria.

Comparative data are presented showing the drug susceptibility to various antibacterial agents of organisms commonly encountered in polymicrobial surgical infections.

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THE INCIDENCE OF MALIGNANCY IN GASTRIC ULCERS BELIEVED PREOPERATIVELY TO BE BENIGN

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THE early diagnosis of gastric cancer and the differentiation between benign gastric ulcer and ulcerating carcinoma of the stomach have perplexed the internist and surgeon for many years. The purpose of this study has been to investigate the clinical and pathologic features of a group of clinically questionable and supposedly benign ulcerating lesions of the stomach that have proved to be malignant when surgical treatment was instituted. The group studied consisted of consecutive cases encountered over a period of 5 years. The cases selected were those in which a diagnosis of benign gastric ulcer had been made; and other cases in which, by various clinical approaches, no definite decision could be reached as to whether a benign gastric ulcer or a malignant ulcerating lesion was present.

REVIEW OF THE LITERATURE

Baillie, and Cruveilhier (14,15) were the first to distinguish between chronic ulcer and cancer of the stomach. In 1857 Brinton emphasized the desirability of discriminating between the cancerous degeneration of the hard margin of an ulcer and the ulceration of a growth originally cancerous. He attempted to prove that cancerous infiltration of a chronic gastric ulcer could occur, and also provided us with a clear description of the process of secondary ulceration in tumors of the stomach. Wilson and MacCarty, in 1909, startled the medical world by a paper in which they stated, "Of the remaining 153 cases, which were undoubted carcinoma, 109 (71 per cent) presented sufficient evidence of previous ulcer to warrant placing them in a group labeled 'carcinoma developing on preceding ulcer.'" Cabot and Adie and Newcomb reviewed the literature relative to the development of cancer on benign gastric ulcer and found a wide variation in the reports: from 1 to 100 per cent. Mallory summed up these reports when he stated that few points in pathology have been more bitterly debated with less result than the subject of the relationship of peptic ulceration and carcinoma of the stomach.

From this question, as to the origin of gastric cancer from previously benign ulcer, developed the necessity of distinguishing between benign and malignant ulcerating lesions. MacCarty and Broders, in 1914, discussed this problem and the most salient fact to them was that the differentiation often is made by a pathologist after the removal of the tissues and not by the clinician or surgeon. Morley studied a series of gastric ulcers removed surgically. To the naked eye they were simple ulcers, but under the microscope 10 per cent were malignant. Gray, Balfour, and Kirklin were of the opinion that about 10 per cent of the benign and malignant ulcers of the stomach cannot be distinguished roentgenologically.

Walters (31) stated that in 1939 gastric resection was performed for malignant lesions of the stomach in 131 cases. The preoperative diagnosis in 109 of these cases was carcinoma of the stomach. The preoperative diagnosis in the 22 remaining cases was as follows: ulcer or ulcerating lesion, probably malignant in 7 cases, ulcerating lesion, malignancy not ruled out in 6 cases, and gastric ulcer in 9 cases.

Steigmann seriously questioned the correctness and value of the usual signs and symptoms thought to be typical of benign and malignant ulcer. Anglem reviewed the records of 192 patients who had carcinoma of the stomach and found that the total average delay from the occurrence of the first symptom

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until a definite diagnosis was made was 17 months. Wangensteen, Tumen, and Alvarez have stated that no reliable clinical criteria are available to differentiate carcinoma from ulcer.

MATERIALS AND METHODS

The material available for this study consisted of records of patients that had been treated at the Mayo Clinic. The initial selection of cases was based on a review of the records of all cases of pathologically proved gastric malignant lesions over a period of 5 years, from 1938 through 1942. These particular years were selected in order to have a suitable follow-up record.

During that period a diagnosis of malignant gastric lesion was made by the surgeon or pathologist at operation in approximately 1,400 cases. It was desired to obtain from this large group all those cases in which the preoperative diagnosis did not correspond to the pathologic diagnosis. All cases were excluded in which a diagnosis of cancer of the stomach or of ulcerating carcinoma had been made by any of the methods of clinical investigation available, such as roentgenologic or gastroscopic examination, or by clinical evaluation. No cases were included in which palpable masses, or any suggestion of extension or of metastatic involvement was noted. If no specimen was removed at operation or if no pathologic material was available for study, the case was not included.

The clinical diagnosis in most cases selected for study was gastric ulcer or ulcerating lesion of the stomach. In the group also were 10 cases in which the preoperative diagnosis was gastric ulcer together with the roentgenologist's statement that malignancy could not be ruled out. In all of the cases studied the lesions were ulcerating in character. Seventy-three cases were selected as the basis of the study.

The specimen removed at operation preserved in formalin was available in each of the 73 cases. Gross characteristics of the lesions were studied, and approximately 460 sections were made and examined carefully.

FINDINGS

Incidence. In the 5 year period, 1938 through 1942, operations were performed on 550 patients who had been given a preoperative diagnosis of benign ulcerating lesion of the stomach. Seventy-three were found to have malignant lesions, an incidence of approximately 13 per cent.

Age and sex. The ratio of males to females was 7.3 to 1. Fifty-two years was the average age for the entire group. The oldest patient was 73 years and the youngest was 25 years old. Forty-four per cent of the patients were 50 years of age or less.

Duration of symptoms. In 71 cases the records gave a specific period from the onset of symptoms to surgical exploration. It averaged almost 38 months. There were 21 patients (28.7 per cent of the entire group) who had been experiencing rather typical ulcer type of dyspepsia from 5 to 40 years.

An attempt was made to determine the clinical progress of symptoms prior to admission. This was accomplished by taking an arbitrary period of 3 months, and checking the progress of symptoms during this period. Forty-seven patients (64.3 per cent) were experiencing a progression in the severity of their symptoms. The number of patients experiencing no change or progression was 17 (23.2 per cent). Nine patients (12.3 per cent) during this 3 month period were having complete relief from their complaints.

Pain. Epigastric pain is the most important and most frequently encountered symptom of benign gastric ulcer and of cancer of the stomach. Pain was the chief complaint of 66 patients. In 40 of the 66 cases the distress was characterized by the periodicity of the uncomplicated peptic ulcer variety. In 26 (39.4 per cent) of the patients the pain could not be described in this sense, but was of constant character, increasing in severity, not rhythmic, and not relieved by antacids or food. One patient experienced seasonal relief, and another had complete relief while on vacation, both shortly before the surgical diagnosis of cancer was made.

Hematemesis and melena. Twenty-one or more than a quarter of the patients in the series stated that they had had one or more gastric hemorrhages sufficient to produce hematemesis, or had noted tarry stools. Only 1 patient had melena without hematemesis.

Emesis. To a moderate or severe degree emesis was noted by 27 of the patients. This symptom was of two types in our cases. In about half of the cases it appeared only occasionally. In the other half of the patients it was severe. When it appeared, it usually persisted, became progressively worse, and was a major symptom. No correlation could be found between the severity of the emesis and the location of the lesion.

Change in weight. The state of the weight was noted in the records of 60 patients. Thirty-four (56.6 per cent) of this group of patients had lost more than 5 pounds (2.3 kgm.). The average loss for these 34 patients was 18½ pounds (8.4 kgm.). It was specifically mentioned in the records of 22 patients that there had been no alteration in weight. Four were actually gaining weight at the time of the initial examination at the clinic.

Gastric analysis. In 66 cases the concentration of free hydrochloric acid in the gastric contents was determined. In 65 per cent of these it was within normal limits (25 to 50 units); in 34 per cent free hydrochloric acid was below normal, and in 21 per cent none was present.

Roentgenologic examination. By and large the entire problem of differential diagnosis of gastric ulcer from malignant ulcerating lesions of the stomach falls on the roentgenologist. Gastroscopic examination is most certainly not a routine procedure even in cases in which the condition is questionable. Thus it is up to the roentgenologist to detect the presence of the lesion, to locate it, and to describe its characteristics in relation to the gastric mucosa and walls.

As Kirklin has written, "Such ulcers designated as benign, without qualifying adjectives are designated so but with the implication that as no marks of malignancy are discerned, the lesions are probably benign, although malignancy cannot be positively excluded . . . for he assumes that every ulcer will be considered as potentially malignant until proved innocent."

One patient was operated on without preliminary roentgenologic examination as the diagnosis was perforated peptic ulcer. The various roentgenologic diagnoses for the 72 patients who had roentgenologic examination have been grouped into ten headings as follows: ulcerating lesion, 8 cases; small ulcerating lesion, 3 cases; gastric ulcer, 13 cases; small ulcer, 13 cases, ulcer 13 cases; gastric ulcer secondary to pyloric obstruction, 2 cases; large ulcer, 6 cases; gastric ulcer, no evidence of neoplasm, 2 cases; ulcer, cannot rule out malignant lesion, 10 cases; ulcerating lesion, should be simple ulcer but unable to rule out malignant lesion, 2 cases. These are, for the most part, broad groups, and they do not serve any exact purpose, except for accuracy in recording.

It should be remembered that these 72 cases have been taken from more than 1,400 cases of surgically verified gastric cancer. The preoperative diagnosis in most cases was made as a result of the findings on roentgenologic examination.

Gastroscopic examination. This was undertaken in 9 of the 73 cases. In 2 of these cases visualization of the ulcer was not possible owing to anatomic difficulties. In 3 cases apparently satisfactory healing and disappearance of a carcinomatous ulcer was demonstrated; in 3 benign ulcers were described, and in 1 the condition was called "chronic gastritis."

Duodenal ulcer associated. In 18 cases (21.9 per cent) of the entire series duodenal ulcer was associated with the gastric lesion. The duodenal ulcer was detected during surgical exploration in 6 cases. In 16 cases the duodenal ulcer was seen on roentgenologic examination. Duodenal ulcer was noted both by roentgenologic examination and at exploration in 5 cases. In 1 case a gastroenterostomy had been performed for obstructing duodenal ulcer, at the Mayo Clinic 6 years previously. In 4 of the cases in this group of associated duodenal ulcers, gastroenterostomy had been performed for treatment of the duodenal ulcer years prior to the diagnosis of gastric ulcer. The gastric acids in the 4 cases were within normal limits.

The duration of symptoms was unusually long in the majority of these cases. Furthermore, in 12 there had been a definite and recorded change in the character of the symptoms, presumably with the development of the gastric ulceration and neoplasm.

The free hydrochloric acid in cases of an ulcerating malignant gastric lesion associated with duodenal ulcer was compared with that in cases of malignant lesion without an associated duodenal ulcer. Twenty-five units or less of free hydrochloric acid were found in 18.7 per cent of those cases associated with duodenal ulcer and in 34.8 per cent of those not associated with duodenal ulcer. An average number of units were found in 43.8 per cent of those with, and in 36.4 per cent of those not associated with, duodenal ulcer.

Medical observations. It could well be emphasized that only 9 of our 73 patients were observed at the clinic for any period of time prior to surgical treatment. These 9 patients (12.3 per cent) were observed at the clinic for 6 weeks to 6 years prior to surgical treatment. All gave evidence of healing, of relief of symptoms, or of disappearance of the ulcer. All others were operated on shortly after the first admission.

Surgical treatment. Partial gastric resection of some type was carried out in 60 (82.2 per cent) of the 73 cases. In 57 one of the modifications of the Billroth II type of partial gastric resection was employed; in 3 the Billroth I type of resection. In 13 (17.8 per cent) of the 73 cases, biopsy or other type of unsatisfactory procedure was performed.

The resectability rate was 82.2 per cent.

Acute perforation. This is uncommon and had occurred in only 2 of our cases. In 1 case perforation occurred while the patient was under observation and material was available for biopsy. In the other case probably the same conditions were present but the events were obtained from the history.

EXAMINATION OF PATHOLOGIC MATERIAL

Pathologic material was available for study in each of the 73 cases in the series. It consisted either of the preserved gross specimen (60 cases) or of biopsy material (13 cases) in instances in which resection had not been performed.

In 72 cases adenocarcinoma was present: in 42 of these the diagnosis was simple adenocarcinoma; in 8 scirrhous adenocarcinoma and in 22 mucous adenocarcinoma. In 1 case the lesion was a lymphosarcoma.

Grading of lesion. Cellular differentiation was studied and the degree of malignancy in the 72 cases of adenocarcinoma was graded according to the method of Broders with the following results: grade 1 in 3 cases; grade 2 in 17; grade 3 in 18; and grade 4 in 34.

Extension. The extension of tumor was classified according to the Dukes classification as modified for the stomach by Dochat in the 72 cases of adenocarcinoma. By this method the extent has been classified into four groups as follows: type A, involvement of mucosa but not beyond, in 12 cases; type B_1, invasion of muscle coats, in 14; type B_2, extension to serosa, in 16; and type C, involvement of regional lymph nodes, in 30.

Thus serosal extension or nodal involvement was present in 63.8 per cent of the cases.

Size of the ulcer. A clinical estimation of the size of an ulcer was given occasionally by the roentgenologist, and this measurement was compared with the recorded findings taken directly from the fresh postoperative material. The postoperative measurement, in most cases, was about two times the size of the estimated roentgenologic dimension.

The smallest ulcer measured was 0.5 millimeter in diameter, and the largest was 8.0 centimeters. Thirty-five per cent were 2 centimeters or smaller; 41 per cent were 2 to 4 centimeters in diameter; and 24 per cent were 4 centimeters or larger.

Location. The location of the ulcer was determined in 64 cases. It was located in the pyloric region in 15 cases; on the anterior wall in 2, on the posterior wall in 8, and on the lesser curvature in 39. No ulcers were found on the greater curvature.

Of the ulcers located on the entire posterior wall, 15 were located near the lesser curvature. Of those located on the anterior wall, 2 were located near the lesser curvature. Therefore 56 (87.5 per cent) were located on or near the lesser curvature.

All of the lesions located in the region of the pylorus were checked for spread of the carcinoma through the mucosa and over into the duodenum. Such spread was found to be present in 5 cases (33.3 per cent) of the cases in which lesions were located in the pyloric region.

Search was made for involvement of perineural lymphatic nodes and in 3 cases such involvement was noted.

SURVIVAL RATES

Of our 73 patients 3 died in the hospital after operation, giving a hospital mortality rate of 4.1 per cent.

Of the remaining 70 patients, all were traced for a period of 3 or more years and 33 (47.1 per cent) lived 3 or more years after operation.

One of the 70 patients could not be traced 5 years after operation. Of the remaining 69 patients, 30 (43.5 per cent) lived 5 or more years.

COMMENT

Walters (30) stated that a roentgenographic diagnosis of benign gastric ulcer was made in 10 per cent of the cases in which operation disclosed carcinoma of the stomach. Finsterer found the incidence to be 21 per cent, and Wangensteen found it to be approximately 10 per cent. In the 5 year period of the study there were 550 surgical patients with a preoperative diagnosis of benign ulcerating lesion of the stomach. Seventy-three lesions were found to be malignant, an incidence of 13 per cent.

Gray, Balfour, and Kirklin stated that for years roentgenologists have emphasized that they cannot distinguish between benign and malignant ulceration in a definite proportion of cases, about 10 per cent in their experience.

Tumen and Bockus indicated that the average age of the patient at onset of symptoms of carcinoma of the stomach was 55 years, and that the average age at onset of symptoms of benign ulcer was 40 years. Fifty-two years was the average age at the time of operation of the patients of this series, and the duration of symptoms before operation averaged 3 years. Thus the average age at the onset of symptoms was 49 years.

In the entire group there were 21 patients (28.7 per cent) that gave a history of ulcer type of epigastric distress of many years duration, from 5 to 40 years. Eusterman and Balfour mentioned this feature of gastric cancer. It is difficult to ascribe the pathologic causation for all of these cases, but in 12 of the 21 cases a duodenal ulcer scar was found by roentgenologic examination or at operation at the time that the diagnosis of gastric cancer was made.

Priestley and Eusterman considered that a fourth of the patients who have malignant gastric lesions will present the so-called peptic ulcer type of history. In this study of ulcerating malignant lesions 60 per cent had pain of classical peptic ulcer character.

Clinical or symptomatic hemorrhage had occurred in 28.7 per cent of our patients. Collins and Knowlton stated that 1.8 per cent of patients with cancer of the stomach had one or more gastric hemorrhages. Blackford and Cole considered the incidence of bleeding in peptic ulcer to be 19 per cent. In 26 per cent of Allen's (2) cases of gastric ulcer hemorrhage occurred. The attitude expressed by Tumen is that a massive hemorrhage from the stomach is strongly suggestive of the presence of a benign lesion.

In 65 per cent of our cases in which the test was made the quantity of free hydrochloric acid in the gastric contents was within normal limits. Walters, Gray, and Priestley stated that 16 per cent of patients who have gastric carcinoma have normal amounts of free hydrochloric acid.

Gastroscopic examinations were made in 9 of the cases, and gave misleading findings in each. Obviously, it is of considerable value in numerous cases not selected as were these. Schindler and Arndal considered gastroscopic examination the best single method for differentiating between benign and malignant ulcers. In their series of 113 cases of gastric ulcer, 19 ulcers were proved benign and 34 malignant. There were 6 incorrect gastroscopic diagnoses and 2 were indefinite. In our cases healing, reduction in size, and even disappearance of malignant ulcers were illustrated on gastroscopic examination.

Steigmann stated that there was an associated duodenal ulcer in 10 per cent of his cases of gastric ulcer and that no such association was found in cases of malignant ulcer, furthermore, that the presence of a duodenal ulcer is a helpful differential point. Wilbur and Rivers found records of 33 cases of gastric carcinoma associated with duodenal ulcer in

the files of the clinic. There were 18 (21.9 per cent) well recorded cases in this study.

Nine patients in our group were observed and treated medically for variable periods of time. Allen (3) has written that 14 per cent of patients treated as having benign ulcer proved to have cancer, and many of these patients apparently responded well to conservative therapy.

The operability rate in our cases was 100 per cent and the resectability rate was 82.2 per cent. This was anticipated from the method of selection. Abrahamson and Hinton found that resection could be performed in 13.7 per cent of all cases in which a diagnosis of gastric cancer was made, and in 38 per cent of those in which the lesion was considered operable.

The findings relative to the microscopic grading of the lesions indicates that, irrespective of the extent or gross characteristics of carcinoma, the degree of cellular differentiation closely corresponds to that found in any group of gastric cancers. These results compare closely with those of Walters, Gray, and Priestley for gastric cancer. A higher percentage of lesions, however, was confined to the mucosa and submucosa.

More than three-quarters of the ulcers were 4 centimeters or less in diameter. It is of interest that Bockus stated that 71 per cent of ulcerating malignant lesions exceeded 4 centimeters in diameter.

Follow-up records were available on 69 of our patients of whom 43.5 per cent lived 5 years or more after operation. Allen and Welch emphasized that the more benign the lesion appears the more likely a final cure. They had performed gastrectomy on 30 patients who had received a preoperative diagnosis of benign ulcer and all of whom proved to have cancer. Their operative mortality was 10 per cent and the 5 year survival rate was 40 per cent.

SUMMARY AND CONCLUSIONS

The study of this series of 73 cases of malignant disease of the stomach illustrates a well defined type of case for which we have no method of diagnosis short of the pathologic examination of the tissues removed. Symptoms, symptom-complexes, signs, laboratory examinations and tests all failed to indicate definitely the malignant or benign nature of these lesions. Even cancers of the stomach behaved in a manner not to be distinguished from benign ulcers when observed and treated medically. The results obtained indicated that the duration of symptoms were usually long; that many of the gastric lesions were associated with duodenal ulcer; and that a high percentage had one or more gastric hemorrhages. Acute perforation of a gastric cancer occurred in the group. Though all lesions were considered operable the resectability rate was 82.2 per cent. Slightly less than half of the patients lived 5 or more years. Of patients operated on for gastric ulcer at the clinic from 1938 through 1942, 13 per cent actually had cancer. Temporizing with an ulcerating lesion of the stomach, therefore, introduces a serious risk.

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PREVENTION OF DEATH FROM EXPERIMENTAL LIGATION OF THE LIVER (HEPATIC PROPER) BRANCHES OF THE HEPATIC ARTERY

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THIS experimental study was undertaken in an effort to elucidate the cause of death which follows ligation of the liver (hepatic proper) branches of the hepatic artery in the dog. The main purpose has been to analyze and evaluate the relative importance of the enzyme lecithinase as the toxic factor responsible for death. Demonstration of the enzymatic properties of the toxins of the clostridium organisms has permitted their direct identification by means of physicochemical methods.

From March 1, 1949, to June 8, 1949, nine dogs were operated upon; morphine-nembutal anesthesia was used and the liver branches of the hepatic artery were ligated but not severed. Six of the 9 dogs died between 24 and 48 hours postoperatively and the postmortem findings, including histological sections of the liver, suggested that death was not always due to acute liver insufficiency. Lecithinase was found in the peritoneal fluid which always accompanied the "liver peritonitis," resulting from ligation of the liver branches of the hepatic artery.

In previous studies (36, 39) on peritoneal exudates of experimental appendiceal peritonitis and experimental intestinal obstruction, it was found that lecithinase was present in sufficient amounts to play a definite and significant role in the production of morbidity and mortality in these experimental diseases. It was also pointed out that the action of antibiotics in aborting the disease process was probably dependent on destroying certain bacteria present in the exudate, thus preventing a synergistic growth necessary for the production of metabolites needed for lethal enzyme production.

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These reasons and the similarities in the pathological picture, in addition to the presence of lecithinase found in the abdominal exudate of dogs dying from ligation of the hepatic proper branches of the hepatic artery, prompted us to treat the dogs with penicillin. Three dogs of the first series were treated with penicillin beginning immediately after surgery and continued for the first 4 postoperative days. One dog survived 10 days; the postmortem examination revealed a bile peritonitis due to the perforation of the gall bladder. The other 2 dogs were sacrificed 7 and 9 months after the operation.

Davis, Tanturi, and Tarkington (4) while studying the effect of reduced blood flow to the liver in experimental renal hypertension used penicillin postoperatively and prevented the death of all dogs in which the hepatic proper branches of the hepatic artery were ligated. Markowitz, Rappaport, and Scott (22a) reported this same fact and have stated that when dogs with totally ligated hepatic arteries are given massive doses of penicillin intraperitoneally and intramuscularly for 1 week, they usually survive, regardless of the absence or presence of the gall bladder. They suggested that the immediate life saving function of the hepatic artery was to maintain oxygen tension at a level incompatible with the proliferation of anaerobes, which are constantly present in hepatic tissue.

The results of our first series of experiments and the conflicting results found in the literature on the same subject led us to investigate thoroughly the problem of the ligation of the hepatic proper branches in the dog.

ANATOMICAL STUDIES

A revision of the anatomy of the arterial supply to the liver of dogs, as compared with

that of man, seemed necessary when one considers that the site of ligation is a main factor in the final outcome (12, 13).

The liver of man and dog is anatomically divided into four lobes; the former is divided into the right and left lobes, the quadrate, and caudate lobes. The right and left lobes of the dog's liver are divided by a deep fissure into two parts, thus creating a medial and lateral portion. Miller calls the medial portion of the right or left lobe of the liver the right or left medial lobe and the lateral portion the right or left lateral lobe. By means of peritoneal reflections and their attachment to the inferior surface of the diaphragm (coronary ligaments), the "bare" area of the human liver comes into existence. The other structure worthy of note is the falciform ligament. This ligament in man represents the ventral portion of the primitive ventral mesogastrium; its superior attachment is the coronary ligament and the inferior, or terminal, attachment is the umbilicus. In the free edge of the falciform ligament is the obliterated (fetal) umbilical vein which is referred to as the round ligament of the liver in the adult. Anatomists consider the falciform ligament the dividing line of the human liver into the right and left lobes.

In contrast to that of the human, the ligaments of the dog's liver vary in two important respects: First, the coronary ligament of the dog, according to Miller, is only an irregular line of peritoneum, which at any point consists only of a single layer of peritoneum. There is then, no "bare" area of the dog's liver comparable to that of the human liver. The second and most important difference is the frequent absence of the falciform ligament, especially in older dogs. Furthermore, the round ligament of the liver is absent except in the young animal.

Arterial supply: 1. Extrahepatic. In the dog, the common hepatic artery courses from the celiac axis, or directly from the abdominal aorta, posterior to the duodenum, approximately 5 to 8 centimeters distal to the pylorus. After reaching the antimesenteric border of the duodenum, this vessel ascends and courses in a transverse, or oblique direction posterior to the portal vein and common bile duct where it terminates in the larger posterior superior pancreaticoduodenal artery and the smaller right gastroepiploic artery. The portion of the common hepatic artery which lies posterior to the portal vein and common bile duct forms a curve with its convex portion directed toward the hilus of the liver. The hepatic proper arteries, usually 4 to 5 in number, arise from the convex portion of the common hepatic artery. These hepatic proper arteries then enter the liver at its hilus and supply the various lobes and their subdivisions.

2. Intrahepatic. Segall's injection experiments on human livers revealed the arterial system to resemble a spreading tree. By injection of the hepatic artery, anastomosis with the phrenic arteries through the subcapsular plexus of the liver were said to occur, first, in the coronary and triangular ligaments; second, in the areolar tissue between the diaphragm and the liver; third, in the "bare" area of the liver, and, fourth, in some instances a branch of the left inferior phrenic artery gave rise to a branch which coursed in the falciform ligament near its attachment to the liver and anastomosed with the intrahepatic branches of the left hepatic proper branch. Injection of the hepatic proper arteries of the dog failed to demonstrate a subcapsular network of anastomosis beneath Glisson's capsule. The hepatic proper arteries were found to give off small branches which coursed with the branches of the portal vein and bile ducts within the liver. Therefore, we believe that since there is no subcapsular arterial network and since there is a marked difference in the type of ligaments of the dog's liver, the avenue for collateral circulation is greatly reduced when compared with that of the human liver. As for the fourth point of possible collateral circulation, as pointed out by Segall, our study failed to demonstrate any connection of the inferior phrenic arteries, or their branches, with the liver branches.

RESULTS OF EXPERIMENTS ON LIGATION OF LIVER BRANCHES OF THE HEPATIC ARTERY

In Table I is summarized the first series of experiments. Dogs were anesthetized with morphine sulfate and intravenous nembutal; the abdomen was shaved, and iodine and al-

TABLE I.—LIGATION OF THE LIVER BRANCHES OF THE HEPATIC ARTERY AND CHOLECYSTECTOMY

Dog No.	Weight kgm.	Date of operation	Survival	Postmortem	Remarks
4	15.8	3–18–49	Less than 48 hrs.	Liver peritonitis	Lecithinase activity in abdominal fluid
5	14.9	3–23–49	Less than 24 hrs.	Liver peritonitis	
6	7.2	4–18–49	Less than 48 hrs.	Liver peritonitis	Smear of liver tissue showed bacteria. Lecithinase in abdominal fluid
7	14.9	4–29–49	24 hrs.	Liver peritonitis	Blood pressure one hour before death=68 mm. Hg.
8	8.1	5–2–49	48 hrs.	Liver peritonitis	
9	6.7	5–5–49	24 hrs.	Liver peritonitis	Lecithinase in abdominal fluid
Penicillin Treatment 300,000 Units Daily During 4 Days					
2	15.8	3–1–49	10 days	Bile peritonitis	
3	12.5	3–16–49	9 months		Sacrificed 1–3–50. Recanalization of hepatic proper branches
10	13.5	6–8–49	7 months		Sacrificed 1–4–50. Recanalization of hepatic proper branches

cohol solutions were used as skin antiseptics. A midline incision of the abdomen was employed. After the peritoneal cavity was entered, the second portion of the duodenum was retracted and traction was maintained with gauze in a caudal direction. The common hepatic artery was freed from the sympathetic plexus and, by means of an untied ligature, traction was maintained in an inferolateral direction. Identification and dissection of the hepatic proper branches, located to the right of the portal vein, was greatly facilitated by the procedure outlined. Each hepatic proper branch was doubly ligated but not transected. The hepatic proper branches to the left of the portal vein were next identified in the space between the portal vein and the common bile duct. An untied traction ligature on this portion of the common hepatic artery allowed us to identify easily and doubly ligate the hepatic proper branches which lie to the left and posterior to the portal vein. The gall bladder was then removed and the abdominal incision closed with silk.

Six dogs were operated upon by means of this procedure and all of the animals died in between 18 and 48 hours. In addition, 2 dogs were operated upon by means of the same operative procedure as outlined, and a third dog was subjected to the same procedure but did not have the gall bladder removed. An arbitrary dose of penicillin (300,000 units 24 hours for 4 days) was given to these animals postoperatively. The third dog died 10 days after the operation and postmortem examination revealed a bile peritonitis due to a perforated gall bladder. The other 2 dogs were sacrificed 7 and 9 months after surgery. These latter 2 dogs were studied to determine the presence or absence of a collateral circulation to the liver. For this purpose a red lead-paste mixture was used. The dogs were sacrificed by bleeding them to death, then a cannula was inserted in the common hepatic artery as it originated from the aorta, or celiac axis. After injection, the vessel was dissected throughout its entire course. In these 2 dogs, which received penicillin and which were subjected to a cholecystectomy and survived, the anatomical study revealed adhesions connecting the lesser curvature of the stomach, first part of the duodenum, and part of the pancreas to the inferior surface of the liver. No injected vessels were seen coursing in the adhesions. Small injected vessels on the ventral surface of the portal vein coursing to the right lobe of the liver were observed and originated from the small branches of the superior pancreaticoduodenal artery. As the hepatic proper branches were not transected, it was observed that recanalization of these vessels had occurred.

In a second series of experiments 14 dogs were divided into 3 groups. The results in the three groups are summarized in Table II. In group 1 (4 dogs), the same operative technique was employed as in the first series of

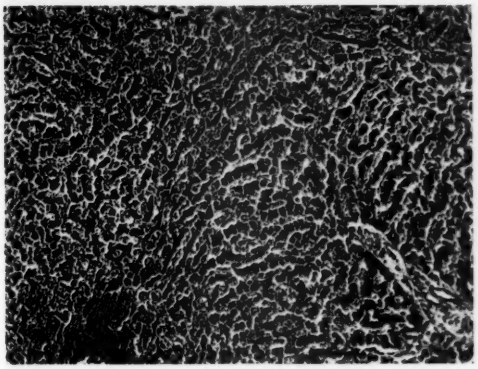

Fig. 1. Photomicrograph of liver of dog 19 which died 26 hours after ligation of hepatic proper arteries showing hyperemia and dilatation of sinusoids. Hematoxylin and eosin stain. ×105.

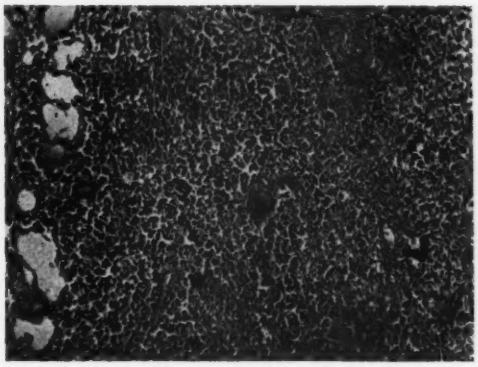

Fig. 2. Photomicrograph of liver of dog 7 which died 24 hours after ligation of hepatic proper arteries, showing complete necrosis of the left lobe. Hematoxylin and eosin stain. ×57.

dogs, with the exception of 1 dog in which a cholecystectomy was not done. In this group, 1 dog died 18 hours after the operation; the 3 other dogs were sacrificed 5 and 7 days, postoperatively. In 2 of the 3 latter dogs (5 days after surgery) postmortem anatomical studies of the common hepatic artery did not reveal any recanalization of the hepatic proper arteries. In 1 of these 2 dogs there were small injected vessels which ascended in the hepatoduodenal ligament. This finding was not observed in the second dog. In the dog sacrificed 7 days after surgery, injection material was observed to pass distally (toward the liver) beyond the ligatures on the hepatic proper branches. This result suggests the possibility of early recanalization and might account for the spontaneous survival of the dog.

In group 2 (7 dogs), the operative technique was modified. In addition to double ligation of the hepatic proper branches, the vessels were transected between the ligatures and cholecystectomy was not done. Four of these dogs died between 20 hours and 4 days after surgery. The 3 remaining dogs were sacrificed 4, 13, and 20 days after surgery. With the exception of 2 dogs, autopsy studies did not reveal any injection material distal to the ligatures. In one exception, a hepatic proper artery had been overlooked at the time of surgery and was not ligated; consequently, there was injection material in this vessel which entered the liver. A variation of origin of the right gastric artery was noted in the second exception of this group. The right gastric artery originated from a hepatic proper artery distal to the point of ligation and transection. Hence, the injected material passed through the small branches derived from the posterior superior pancreaticoduodenal artery, which coursed over the first portion of the duodenum, and connected with the right gastric artery. In this group it was definitely observed that the small vessels occasionally injected in the hepatoduodenal ligament were supplied by small branches from the posterior superior pancreaticoduodenal artery.

In group 3 (3 dogs), the same procedure was used as in group 2 with the addition of a cholecystectomy and ligation with transection of the right gastric artery. These 3 dogs died 24 hours after operation. Postmortem studies were not done on these animals.

In order to perform physiologic studies, which would complement the above two studies, 11 dogs were subjected to ligation and section of the hepatic proper branches and the right gastric artery. In addition, a cholecystectomy was performed. Eight of the 11 dogs died 18 to 55 hours postoperatively. Three dogs survived and were sacrificed 13 and 15 days after surgery. In these 3 dogs no arterial circulation to the liver was demonstrated at postmortem. In addition to the above surgical procedure, the posterior superior pancreaticoduodenal artery was ligated near its

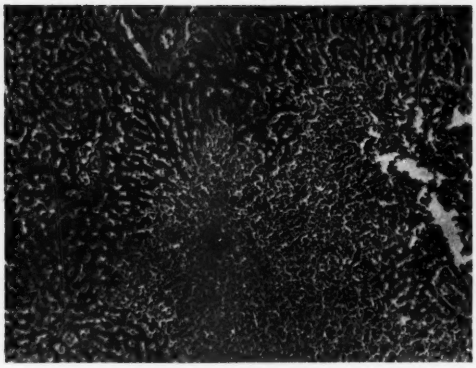

Fig. 3. Photomicrograph of liver of dog 6 which died 48 hours after ligation of hepatic proper arteries showing a hemorrhagic infarct. The smear of liver tissue demonstrated bacteria with the characteristics of anaerobic rods. Hematoxylin and eosin stain. ×62.

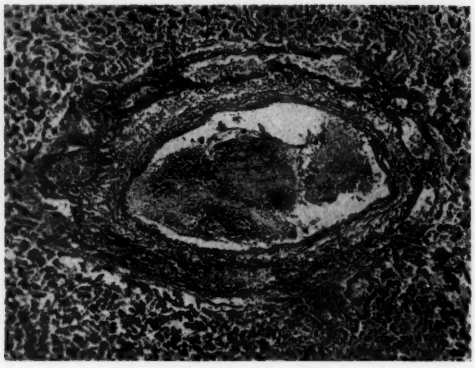

Fig. 4. Photomicrograph of left lobe of the liver of dog 21 which died 3 days after ligation of hepatic proper arteries. Thrombosis and destruction of the wall of a branch of hepatic vein and necrosis of liver cells are seen. Hematoxylin and eosin stain. ×53.

origin from the common hepatic artery in 4 of the 11 dogs, one of which survived.

BLOOD CHANGES AFTER LIGATION OF THE HEPATIC ARTERY

Studies were made upon prothrombin concentration in the plasma (37); acid and alkaline phosphatase in the serum (10); total serum proteins (28); glucose (29), and hematocrit in these animals. The dogs were operated upon in the morning and postoperatively samples of blood were taken every 26 hours. Since some of the dogs died the second postoperative night, the blood changes found the second postoperative morning might not correspond with the blood alteration during the latest hours of survival. Therefore, a group of 6 dogs were operated upon and followed closely through their course in order to obtain samples of blood when they were near death. The total number of dogs studied was 17 and in Tables III and IV the results are summarized. Nine of the 17 dogs died between 19 and 72 hours after surgery. The dogs which survived were sacrificed at different periods for the anatomical studies of the hepatic artery.

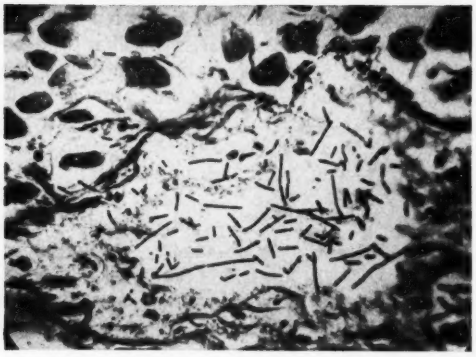

Fig. 5. Photomicrograph of liver of dog 16 which died 20 hours after ligation of hepatic proper arteries showing bacteria having the characteristics of anaerobic rods. Hematoxylin and eosin stain. ×172.

Prothrombinemia. Variations in the prothrombinemia were seen to decline progressively in all the animals which died. In those animals which survived, a decrease of the prothrombin concentration in plasma was observed 24 to 48 hours after surgery; thereafter, the concentration rose to the preoperative level. In this experiment, as in others previously published (40), the prothrombinemia was a very sensitive test in detecting a hepatic injury. The decrease in prothrombin very rarely reached hemorrhagic levels. Hemorrhage was never found to be the cause of death and the impression was gained that other pathological changes occurred elsewhere which could account for the death of the animals. This is confirmed in the results as seen in Table IV, in which the prothrombin studies were done at the time of death. The lowest concentration in this group was 16.1 per cent

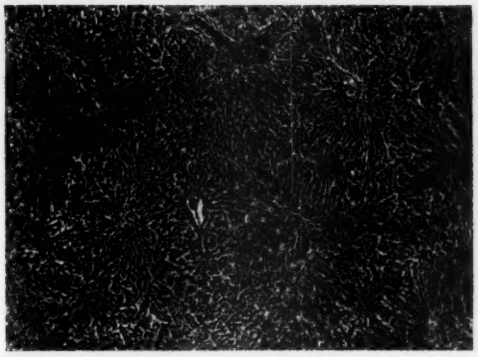

Fig. 6. Photomicrograph of liver of dog 101 which died 55 hours after ligation of hepatic proper arteries showing hyperemia and architecture still well preserved. Hematoxylin and eosin stain. ×30.

Fig. 7. Photomicrograph of liver of dog 31 sacrificed 13 days after ligation of hepatic proper arteries showing central and midzone necrosis and normal hepatic cells in the portal spaces. Hematoxylin and eosin stain. ×30.

and postmortem studies showed no hemorrhagic tendency. However, a closer scrutiny revealed that the liver was undergoing rapid pathological changes, if one considers that lower levels of prothrombin were found at the time of death.

Phosphatasemia. The interpretations of the results in the alkaline phosphatase activity in serum must be considered in regard to the fact of whether or not the gall bladder was removed (5). It is known that cholecystectomy alone produces an increase in the alkaline phosphatase in normal dogs; the increase is greater than in experiments in which hepatotoxic drugs are used, but less than in experimental biliary obstruction. The maximal level is observed between the 10th and 16th day following cholecystectomy in the normal animals. After a variable period of time, a decline begins which eventually reaches the normal level. In the present series of dogs in which the hepatic artery was ligated the gall bladder was removed in all but 7 dogs. Three of these dogs died and in all 3 the alkaline phosphatase activity was considerably increased. In the 4 dogs that survived only 1 showed a significant increase; however, another dog of the surviving group showed a slight increase the 4th postoperative day but this increase declined toward the normal activity 5 days postoperatively. The gall bladder was removed in 10 dogs, in addition to hepatic artery ligation, and 6 of these dogs died. In 2 of the animals that died, a considerable increase of the alkaline phosphatase activity was observed. In the 4 remaining animals, the determination of the alkaline phosphatase activity was not performed because the samples of serum were considered inadequate due to a high degree of hemolysis. In the 4 dogs that survived, 2 showed a considerable increase in the alkaline phosphatase activity; 1 revealed no change in this enzymatic activity, and in 1 dog the alkaline phosphatase activity was not determined. In general it can be stated, that our experiments revealed the highest levels of alkaline phosphatase activity in dogs that did not survive. Even with this finding one is un-

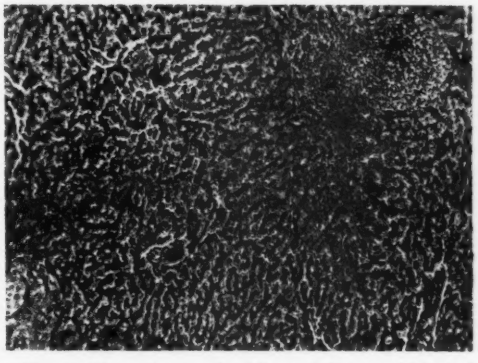

Fig. 8. Photomicrograph of liver of dog 32 which died in coma, 24 hours after ligation of hepatic proper arteries showing hyperemia and small abscesses. Hematoxylin and eosin stain. ×55.

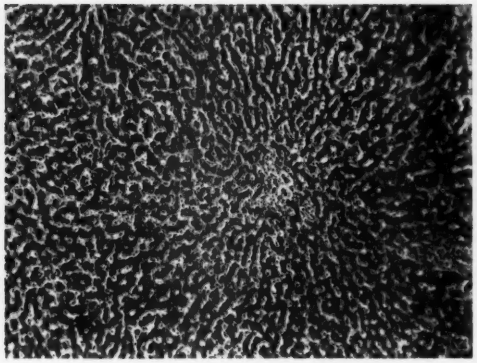

Fig. 9. Photomicrograph of right lobe of the liver of dog 21 which died 3 days after ligation of hepatic proper arteries showing generalized cloudy swelling of hepatic cells. Hematoxylin and eosin stain. ×57.

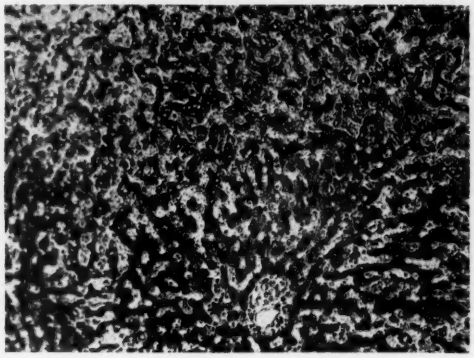

Fig. 10. Photomicrograph of liver of dog V, male, 45 pounds in weight, which received 50 units per pound of alpha-toxin intravenously, by the drip method. Total toxin injected: 750 units. The dog died 2¾ hours after injection and showed hypoglycemia and hypoprothrombinemia at the time of death. Hyperemia and necrosis of liver cells are present. Hematoxylin and eosin stain. ×110.

able to state with certainty the quantity of liver damage produced.

Serum proteins and hematocrit. The trend of serum proteins show a progressive decline; however, this finding is not considered significant. The hematocrit shows a decrease in the dogs that survived and a progressive increase in those animals that died. As a matter of fact, if compared with the preoperative levels, hemoconcentration was found in all of the dogs at the time ot death. The hematocrit decrease found in the dogs that survived could be interpreted as due to an anemia but does not permit one to draw conclusions about the changes in the serum proteins.

Hemolysis. Hemolytic plasma was observed very rarely in the dogs that survived, although it was a conspicuous finding in samples obtained from dogs near the time of death and in all the dogs that died. The presence of hemolysis and hemoconcentration was very remarkable as this coexistence was always observed in the dogs that died. Both of these findings were then more remarkable when they were compared with the hemodilution found in the animals that survived. It may be possible that the arterial supply to the liver was related with the mechanism of blood cell formation since a decrease in the hematocrit reading was always found in the very late postoperative period.

Glucose. A slight variation in glycemia was revealed in the animals that survived. On the other hand, hypoglycemia was always found in the dogs that died. This finding was almost constant in the blood samples taken at the time of death (Table V). At this particular period all dogs exhibited the following symptoms; dyspnea, convulsions or twitchings, vomiting, and comatose state. Our results agree with those of Collins, Shelling, and Byron and of Huggins and Post, who stated that ligation of the arterial supply to the liver of dogs caused hypoglycemia and convulsions before death. We have not administered glucose to see if it would prevent convulsions and prolong life. As we have found slight variations in the glycemia, but not hypoglycemia, in the dogs that have survived and in which anatomical studies have demonstrated no arterial supply to the liver, we presume that hypoglycemia must be related with some other factor rather than lack of arterial supply to the liver per se.

COURSE, PATHOLOGY, AND LIVER HISTOLOGY

Regardless of the operative technique used (simple ligation or ligation and section of all hepatic proper branches with or without cholecystectomy), all the dogs that died presented the following symptoms during their postoperative course; hyperthermia, depression or lethargy, tachycardia, hypotension, and ocular

Fig. 11. Photomicrograph of adrenal cortex of dog V. The architecture is distorted and glomerulosa and fasciculata layers show disappearance of sudanophilic granules. Lipoid stain (Mallory). ×40.

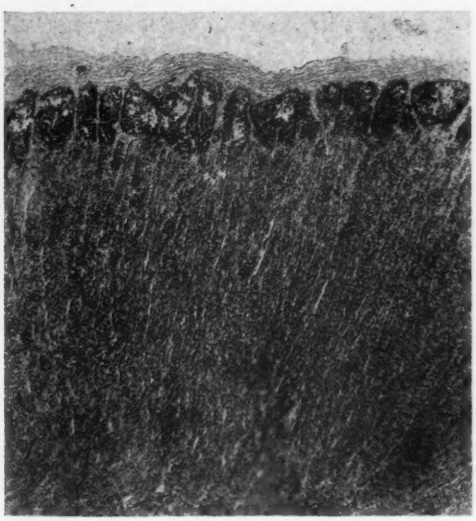

Fig. 12. Photomicrograph of adrenal cortex of dog 18 which died 3 days in hypoglycemic coma after ligation of hepatic proper arteries. Hemolytic fluid was found in the abdominal cavity. Sudanophilic granules are still present in the glomerulosa; the fasciculata and reticularis layers are depleted. Lipoid stain (Mallory). ×40.

congestions. After recovery from the anesthetic, the dogs stood in their cage for a variable period of time, then they became depressed, lay down, and responded poorly to external stimuli. Eventually their depression passed into a state of lethargy and dyspnea; twitchings of isolated muscular groups or generalized convulsions were observed and finally, a comatose state was reached. Blood samples obtained at this time were always hemolyzed; sometimes the plasma was icteric but jaundice seldom was observed. Some dogs did not recover from the anesthetic and died 17 hours after surgery. This was the shortest survival period observed in our series of experiments. The postmortem findings observed immediately after death, or when the dog was sacrificed during its terminal state, consisted of various quantities of hemolytic, sometimes purulent, thin fluid in the abdominal cavity. All the viscera were congested and the stomach, duodenum, and intestines were without their normal glistening appearance. The liver revealed a fibrinous exudate over all its surfaces. The lobes of the liver varied in their gross appearance; at times distinct greenish-purple colored areas were noted and occasionally, the liver edges were gangrenous. On sectioning the liver surface, the parenchyma appeared congested and edematous. Occasionally a uniform yellow color revealed what would appear to be a fatty degeneration; the delimited or infarcted zones were not difficult to recognize but central abscesses were rarely found. In a few cases in which the superior pancreaticoduodenal artery had been ligated, the first portion of the duodenum was dilated and the pancreas was edematous and congested. Petechiae and small hemorrhages were seen on the peritoneal surface of this latter organ. All the animals which survived 48 hours or longer and then succumbed showed the same pathological picture.

We have observed most of the histological changes, as described in the literature, in the liver of dogs that died. These changes consisted of hyperemia (Fig. 1), due to dilatation of vessels in the infarcted area (acute congestion), edema, agglutination of erythrocytes, cloudy swelling progressing to complete necrosis (coagulation necrosis, Fig. 2), and con-

TABLE II.—LIGATION OF THE LIVER BRANCHES OF THE HEPATIC ARTERY WITH OR WITHOUT CHOLECYSTECTOMY

Dog No.	Sex Weight kgm.	Date of operation	Cholecystectomy	Symptoms	Survival	Postmortem	Remarks
1st Group							
1	Male 11.2	9-22-49	Yes	Hyperthermia, icteric plasma, dyspnea, hemolytic plasma, lethargic	Sacrificed 9-29-49 (7 days)		Hepatic proper arteries ligated but not transected. Injection of material distal to ligature
2	Male	9-22-49	Yes	Hyperthermia, depression, lethargic, hemolytic plasma	Died 18 hrs.	Liver autolysis Hemolytic fluid in abdomen (100 c.c.) general congestion	
3	Male	9-28-49	Yes	No major symptoms, plasma limpid	Sacrificed 5 days after surgery	Some exudate organized in the surface of the liver	Small injected vessels ascending in hepatoduodenal ligament. No injection material distal to ligature
4	Male 11.2	9-28-49	No	Hyperthermia, limpid plasma	Sacrificed 5 days after surgery	Not much pathology	No injection material distal to ligatures. No fine vessels in hepatoduodenal ligament
2nd Group—Double Ligation and Transection of the Hepatic Branches							
5	Male 9	10-4-49	No	Hyperthermia, plasma clear	Sacrificed 20 days after surgery	No pathology	No injection material distal to ligatures. Few injected fine vessels in hepatoduodenal ligament. These arose from right gastric artery
6	Female 11.2	10-4-49	No		Died 20 hrs. after surgery	Liver autolysis Peritonitis Intestinal distention	The portal vein was injured during the operation and repaired. The pancreaticoduodenal was ligated too but not severed
7	Male 9	10-11-49	No	Hyperthermia, plasma clear	Sacrificed 13 days after surgery	Postmortem	One hepatic proper artery overlooked and not ligated
8	Female 10	10-11-49	No	Hyperthermia, tachycardia, hemolytic and icteric plasma	Died 3 days after surgery	Liver autolysis Peritoneal hemolytic fluid	The pancreaticoduodenal had to be ligated. A careful dissection was performed. The celiac trunk was injected with dye and it could be easily found that no arterial supply to the liver persisted. The phrenic abdominal arteries were injected through the aorta and no collateral through the liver was found
9	Male 7	10-17-49	No	Plasma icteric Depression Jaundice	Sacrificed when appeared very sick, 4 days after the operation	Bile peritonitis due to perforated gall bladder Liver autolysis	
10	Male 7	10-17-49	No	Hyperthermia, plasma clear, no symptoms	Sacrificed 4 days after surgery	No major pathology	No visible arterial supply to the liver. No vessels in hepatoduodenal ligament
11	Female 10	11-1-49	No	Depression, hypertension, hyperthermia, plasma hemolytic	Died 3 days after surgery	Peritonitis 200 c.c. of purulent hemolytic fluid Liver autolysis. When a section of liver was taken bubbles of gas were observed Right and left lobes biopsy. Right lobes were less necrotic than the left ones. Gall bladder in the way of gangrene	The pancreaticoduodenal had to be ligated before its bifurcation but was not severed. No injection matcrial distal to ligatures. No vessels in the hepatoduodenal ligament. However, right gastric connected with a hepatic proper artery distal to ligatures. Above vessels coursed posterior to bile duct and portal vein
12	Male 8	11-1-49	Yes	Hyperthermia, plasma slightly icteric	Sacrificed 27 days after surgery	Perihepatitis	No injection material distal to ligatures. Many small vessels in hepatoduodenal ligament. Connected with small branches from superior pancreaticoduodenal.
3rd Group—Double Ligation and Transection of Hepatic Vessels and the Right Gastric Artery Above the Pylorus							
13	Female 13.500	11-21-49	Yes	Depression, lethargic	Died after surgery 24 hours	Liver autolysis	The pancreaticoduodenal had to be ligated
14	Female 15.800	11-21-49	Yes	Lethargic	Died 24 hours after surgery	Liver autolysis, bloody purulent fluid in the abdomen	The pancreaticoduodenal had to be ligated
15	Female 16.800	12-12-49	Yes	Depressed	Died 24 hours after surgery	Hemolytic fluid in abdomen	When dog was moribund it was opened to collect lymph from cisterna. Lymph was hemolytic

TABLE III.—BLOOD CHANGES AFTER LIGATION OF LIVER BRANCHES OF HEPATIC ARTERY

Dog No.	Sex Weight kgm.	Time after ligation	Pro-thrombin per cent	Phosphatase		Proteins gm. per cent	Glucose grams per cent	Hemolysis	Hematocrit per cent	Remarks
				Alkaline	Acid					
1	Male	0	108	1.65	0	5.8	0.81	N	39.2	Gall bladder removed. Sacrificed 7 days after operation. Hepatic proper arteries ligated but not transected. Injection material distal to ligature
	11.2	17 hrs.	57.0	8.28	0.23	6.1	0.72	N	45.2	
		22 hrs.	69.5	14.10	—	5.3	0.68	P	43.3	
		41 hrs.	49.5	19.00	—	5.4	0.86	P	38.5	
		65 hrs.	50.0	20.00	0.17	—	0.85	P	33.7	
		89 hrs.	57.0	—	—	—	1.00	N	31.4	
		7 days	93.0	33.00	0.46	4.2	0.86	N	26.7	
2	Male	0	92.0	3.13	0.103	6.17	1.21	N	39.8	Gall bladder removed. Died 2 hrs. after sample was taken
	11.2	17 hrs.	65.0	9.55	0.25	—	0.62	P	53.0	
3	Male	0	259	0.57	0.26	5.9	0.80	N	39.6	Gall bladder removed. Sacrificed 5 days after ligation. Small injected vessels ascending in hepatoduodenal ligament derived from right gastric. Injection material distal to ligature on hepatic proper arteries
	10	17 hrs.	133	2.3	0.24	6.07	0.96	N	49.5	
		41 hrs.	116	1.68	0.16	5.7	1.03	N	45.2	
		65 hrs.	173	2.04	0.206	5.7	0.91	N	44.5	
4	Male	0	129	0.50	0.54	5.6	0.85	N	43.3	Gall bladder left. Sacrificed 5 days after ligation. No injection material distal to ligatures. No fine vessels in hepatoduodenal ligament
	11.2	17 hrs.	82	2.38	0.15	6.0	0.78	N	46.5	
		41 hrs.	59.5	6.75	0.05	5.83	0.68	N	43.2	
		65 hrs.	64.0	12.9	0.206	5.4	0.72	N	39.4	
5	Male	0	44.2	3.18	0.103	4.7	0.84	N	33.7	Gall bladder left. Sacrificed 19 days after ligation. No injection material distal to ligated hepatic proper arteries. Few injected fine vessels in hepatoduodenal ligament arose from right gastric artery
	9	17 hrs.	39.3	3.60	0.172	4.7	1.03	N	33.3	
		41 hrs.	46.0	3.30	0.130	4.5	0.84	N	29.9	
		65 hrs.	56.2	2.73	0.195	4.6	0.80	N	26.2	
		6 days	60.6	2.25	0.138	4.8	0.73	N	25.0	
		19 days	73.0	1.18	0.149	4.5	0.72	N	31.4	
7	Male	0	134	0.64	0.275	6.4	0.71	N	41.0	Gall bladder left. Sacrificed 13 days after ligation. One hepatic proper branch overlooked at surgery not ligated and transected
	9	17 hrs.	61	1.89	0.300	6.8	0.89	N	51.5	
		41 hrs.	76	3.48	0.332	6.4	0.83	N	47.7	
		65 hrs.	89	4.20	0.126	6.3	0.92	N	43.2	
		12 days	101	2.19	0.206	6.1	0.72	N	38.3	
8	Female	0	117	0.70	0.24	5.9	0.64	N	47.6	Gall bladder left. Found dead 3 days after ligation
	10	17 hrs.	98	3.30	0.34	6.4	0.83	N	54.7	
		41 hrs.	48	7.75	0.36	5.3	0.82	N	52.4	
9	Male	0	103	1.62	0.286	6.43	0.85	N	21.1	Gall bladder left. Sacrificed 4 days after ligation. Not possible to check hepatic proper branches to liver because of friable tissue. Peritonitis present due to perforated gall bladder
	7	17 hrs.	46	7.64	0.424	5.9	0.76	N	24.2	
		65 hrs.	40	33.0	0.57	5.0	0.68	N	24.5	
		4 days	36.4	52.7	0.56	4.4	0.81	N	24.3	
10	Male	0	114	3.21	0.264	5.4	0.86	N	38.3	Gall bladder left. Sacrificed 4 days after ligation. No visible arterial supply to the liver. No vessels in hepatoduodenal ligament
	7	17 hrs.	80	1.63	0.286	5.0	1.03	N	36.8	
		65 hrs.	109	4.06	0.230	4.4	1.01	N	32.5	
		4 days	92.4	3.12	0.172	4.4	0.82	N	29.1	
11	Female	0	93.4	1.87	0.172	4.9	0.79	N	35.1	Gall bladder left. Died 3 hrs. after sample was taken. Excessive blood loss at time of surgery. Portal vein damaged. No injection material distal to ligatures
	10	24 hrs.	74.1	5.4	0.6	5.6	0.99	N	38.2	
		48 hrs.	86.3	11.0	0.184	4.6	0.85	N	36.0	
		72 hrs.	54.1	31.2	0.435	—	0.76	N	50.0	
12	Male	0	85.5	0.87	0.15	5.6	0.74	N	52.0	Gall bladder removed. Sacrificed 27 days after surgery. No injection material distal to ligature
	8	24 hrs.	87.2	5.64	0.10	6.0	0.82	N	55.0	
		48 hrs.	108.6	9.30	0.115	5.07	0.78	N	49.1	
		72 hrs.	95.0	16.0	0.275	—	0.93	N	50.6	

siderable engorgement of the sinusoids. Either hemorrhagic or anemic infarcts were seen, although, the characteristic feature of the early stages was more of the nature of hemorrhagic infarcts (Fig. 3). Thrombosis of the branches of hepatic and portal veins (Fig. 4), edema, and necrosis of bile ducts with extravasation of bile was also observed. Dogs which were sacrificed in the morbid state revealed bacteria, having the characteristics of anaerobic rods (Fig. 5) occupying the vessels or the intercellular spaces. This finding demonstrated that proliferation of bacteria had taken place in the liver. On the other hand, there are instances in which death could not be explained on the basis of the liver histology (Fig. 6, dog

101). The dogs which were sacrificed 7 or 13 days after surgery presented a picture of central and midzone necrosis with a preserved row of swollen but normal hepatic cells, in the portal spaces (Fig. 7). This aspect is similar to that seen in experimental toxic necrosis in the dog's liver (chloroform) during the early period of recovery. Leucocytes were not found entering the necrotic areas, consequently, we cannot say that some of the changes seen are of the acute inflammatory type. Even in those preparations in which small abscesses were observed (dog 32), leucocytes were absent (Fig. 8). As we have pointed out before, there were differences between the gross appearance of the various lobes of the liver. Likewise, the histological picture varied in the different lobes of the liver when they were compared. For example, the left lobe of dog 21, which died 3 days after surgery, revealed histologically almost a complete necrosis with necrosis of the wall of the vessels and thrombosis; bacteria were also seen (Fig. 4). The right lobe of this dog revealed only a generalized cloudy swelling of the hepatic cells (Fig. 9). This difference is explained by the fact that in the postmortem anatomical study the right gastric artery originated from a hepatic proper branch distal to our ligature; consequently, the right lobe still received arterial blood.

Some of the conflicting results found in the literature may be explained on the basis that acute ligation of the liver branches of the hepatic artery in the dog is not always fatal, as is shown by our spontaneous survivals of 31.3 per cent. Since we have additional anatomical proof that no arterial supply was left intact, it may be concluded that the dog's liver can survive the loss of its arterial supply.

In the dogs in which ligation was followed by death (68.7 per cent in our series), the outcome appeared to be directly related to liver autolysis; the lethal effect of which has been explained by Ellis and Dragstedt as being due to infection by anaerobic bacteria of the Clostridium welchii type normally present in the livers of grown dogs. In the past, the presence of these bacteria, which are needed for the formation of toxic products, has been largely demonstrated in in vivo experiments on liver autolysis.

The following seven findings, in addition to our results in the penicillin treated dogs, confirm the view that, besides the ligation of the hepatic branches per se, bacteria and their toxins play an important role in the mechanism of death.

1. The always present hemolytic abdominal fluid found in various quantities in the dogs which died from the ligation of the hepatic proper branches.

2. The lecithinase present in the abdominal exudate.

3. The survival of some of the dogs in which anatomical studies demonstrated that all the arterial supply of the liver had been abolished.

4. The rod-shaped bacillus, with all the characteristics of anaerobic bacilli, present in the liver of the dying dogs.

5. The hemolytic plasma which almost constantly was found at the time of death.

6. The short life and the rapid changes which took place in the liver, revealed by the pronounced hypoprothrombinemia, hyperphosphatasemia, hypoglycemia, and the hemoconcentration found in the morbid animals, in contrast to the findings in those animals which survived.

7. The fatal outcome which occasionally occurred even though the pathological picture of the liver offered no explanation for death.

The factor which appeared to play the most important role in the cause of death was lecithinase. As is shown in Tables I and IV, the presence of lecithinase was found in the abdominal exudate in those animals which succumbed. This is very significant since attempts to identify this enzyme in blood was always negative in the hands of the other investigators (20). Furthermore, utilizing the turbidimetric measurement, we have demonstrated that hemolyzed saline washed blood cells have a strong inhibitory action on the activity of lecithinase (39). This is significant, because every exudate removed from the experimental animals contained a considerable percentage of hemolyzed blood cells.

Clostridium perfringens is stated to produce several exo-enzymes capable of hydrolyzing a variety of substrates, namely, lecithin and sphingomyelin (16, 17, 19), hyaluronic acid

TABLE IV.—LIGATION AND SECTION OF LIVER BRANCHES OF HEPATIC ARTERY, RIGHT GASTRIC ARTERY ABOVE THE PYLORUS AND CHOLECYSTECTOMY. BLOOD CHANGES AT THE TIME OF DEATH

	Sex Weight kgm.	Date of operation	Hematocrit per cent	Glucose gm. per cent	Proteins gm. per cent	Alkaline phosphase	Pro-thrombin per cent	Remarks
Dog 101	M.	2-13-50						Gall bladder removed. Last sample taken a few minutes before death. Highly hemolyzed sample inadequate for proteins and phosphatase determination. The hemolyzed abdominal fluid was tested for lecithinase activity. Test: +
Before operation	9		45.9	0.69	5.6	1.36	145	
55 hrs. after surgery			77.0	0.82	—	—	16.1	
Dog 102	M.	2-13-50						Gall bladder removed. Died 10 minutes after drawing last sample, which was hemolyzed. Hemolytic fluid in abdomen: Test for lecithinase activity: +
Before operation	10.7		51.0	0.84	6.6	0.94	100.5	
24 hrs. after surgery			67.3	0.31	—	7.5	22.0	
Dog 103	M.	2-15-50						Gall bladder removed. Died 10 minutes after drawing last sample, which was highly hemolyzed. Hemolytic fluid in abdomen. Test for lecithinase activity: ±
Before operation	11.2		51.5	0.73	5.4	0.9	135	
24 hrs. after surgery			67.3	0.30	—	—	26.6	
Dog 104	M.	2-20-50						Gall bladder removed. Died 3 days after surgery. Last sample taken 10 minutes before death. Hemopurulent peritonitis, hemolytic and icteric plasma
Before operation	9		48.0	0.79	6.57	1.24	141	
3 days after surgery			60.0	0.64	—	—	43.4	
Dog 105	F.	2-20-50						Gall bladder removed. Died overnight
Before operation	11		46.5	0.81	5.5	0.6	93	
Dog 106	M.	2-21-50						Gall bladder removed. Sacrificed 13 days after surgery.
Before operation	13.5		51.0	0.74	6.2	1.07	144.5	

(24, 25), collagen (18, 30), glycogen or starch (9, 35), ribonucleic acid (35), gelatin (23), and others. Lecithinase, haluronidase, and collagenase are considered responsible for the physiological and pathological effects of crude Clostridium perfringens culture filtrates (8). The lecithin-splitting enzyme is considered the main lethal factor and has been identified with the alpha-toxin of Clostridium perfringes (type A) organisms (17, 19), whose properties appear to correlate well with their ability to produce this toxin (7). The roles played by the individual enzymes in infections due to Clostridium perfringens has not been ascertained with certainty; however, the principal function of the enzymes in promoting the growth of Clostridium perfringens in vivo has been tentatively outlined (34).

The lecithinase serves to disrupt the cell membranes of various cellular elements of the tissue, including the phagocytic cells, and makes the cells accessible to the other enzymes substrates. Furthermore the lecithinase, as a result of its action on protein lipid complex in the muscle, frees appreciable amounts of various lipids (8, 18, 32), some of which serve to stimulate the formation of more lecithinase, as purified lecithin has been found to do (1). Robb-Smith and Frazer and associates studied the action of crude Clostridium perfringens toxic filtrates on tissue. The former concluded that the histological changes found in muscle, in gas gangrene due to Clostridium perfringens, could be produced in vitro with culture filtrates, with the exception of edema and gas formation. Frazer noted that a visible breakdown of connective tissue occurred before any effect on muscle was noted. Tendon and nerve were more resistant than other tissue; however, with longer exposure these two structures were effected. Dilatation and thrombosis of the microscopic blood vessels were regularly seen, as was swelling of the vascular endothelium. It appeared that both the collagenase and lecithinase aided in the destruction of capillaries.

Type A filtrates were injected by Goertzen into rabbits, guinea pigs, and mice. Hemolysis was observed only in the mice and only when they survived longer than 6 hours. Histologically, he found cloudy swelling of all organs, particularly of the kidney; hemoglobin cylinders were observed in the kidneys.

Zamenick and associates studied the physiologic action of Clostridium perfringens (type A) in dogs by injecting glycerol dialyzed toxin filtrate, and more purified lecithinase and hyaluronidase. They found that a number of

TABLE V.—LIGATION AND SECTION OF LIVER BRANCHES OF HEPATIC ARTERY, RIGHT GASTRIC ARTERY, AND CHOLECYSTECTOMY

Blood Changes at the Time of Death

Dog No.	Sex Weight, kgm.	Date of operation	Glucose gm. per cent	Hemolysis	Remarks
18	F.	1-10-50			Died while drawing last sample
Before surgery	9		0.90	—	
24 hrs. after surgery			0.87	+++	
3 days after surgery			0.33	++++	
19	F.	1-10-50			Died 2 hours after drawing last sample
Before surgery	7.6		0.86	—	
24 hrs. after surgery			0.47	++	
20	M.	1-10-50			Sacrificed 15 days after surgery. No arterial circulation to the liver found
Before surgery	9		0.89	—	
19 hrs. after surgery			0.89	—	
3 days after surgery			0.94	—	
4 days after surgery			1.01	—	
21	F.	1-12-50			Sacrificed 13 days after surgery. No arterial circulation to the liver found
Before surgery	6.7		0.69	—	
24 hrs. after surgery			0.83	—	
2 days after surgery			0.79	—	
22	M.	1-12-50			Died soon after last sample was taken
Before surgery	10		0.72	—	
24 hrs. after surgery			0.48	+++	

characteristics of the syndrome of traumatic shock may be produced by Clostridium perfringens (type A) toxic filtrate given either intramuscularly or intravenously. Intravenous injection was followed by intravascular hemolysis, decline in cardiac output and blood pressure, increase in prothrombin time, edema and hemorrhage into the lungs and small intestine, and congestion of the liver, spleen, and kidneys. The action of the toxic filtrate, administered either intravenously or intramuscularly, was consistent with the damaging effect as might theoretically be expected by the lecithinase component on cell surfaces. In the case of the erythrocytes, the result was rupture of the cell wall; in the case of the vascular endothelium the result was leakage of whole blood or plasma through a damaged membrane. The possibility that effects ascribed to the toxins might be due to substances used in the bacterial culture media has been ruled out by the prevention of this toxic effect both by active immunization of animals and by administration of antitoxin in advance of the toxin. The fact that Zamenick and associates were able to protect mice and dogs from a lethal intravenous dose of Clostridium perfringens filtrate, through the injection of purified lipid preparations hydrolyzable by Clostridium perfringens lecithinase, seemed to indicate that this enzyme was the principal toxic component of the filtrate. Theoretically, the excess of lipids injected would, by a substrate partition effect, prevent the action of the lecithinase on the tissue. This theory was supported by the finding that lecithin and antitoxin compete for the lecithinase (45).

EFFECT OF INTRAVENOUS INJECTION OF ALPHA-TOXIN IN THE DOG

A series of 19 dogs were anesthetized with nembutal and both femoral veins were exposed in order to facilitate the intravenous injection of the toxin and the withdrawal of blood samples. The toxin used in our experiments was a Clostridium perfringens (type A) culture filtrate and assaying 200 mouse minimum lethal doses per milliliter. Its histamine content was determined and found to be 1 gamma per milliliter. The required amount of filtrate was diluted to 200 milliliters with sterile saline and injected intravenously into dogs by a continuous drip method, over a period of 2 to 3 hours. The dosage varied from 8 to 75 mouse minimum lethal doses per pound of body weight. The blood glucose level, the prothrombin time, and the absence, or presence, of hemolysis were recorded throughout the experiment. Sections were taken of the adrenal and liver of the animals that died. The adrenals were fixed in formalin for 24 hours and Mallory's technique for lipoid stain of the adrenal cortex was used. The liver

sections were stained with hematoxylin-eosin stain. The results are shown in Table VI.

The injection of toxin was always followed by death of the animal in a few hours when the dosage exceeded 50 minimum lethal doses per pound; below this level the time of death varied. A dose as small as 8 minimum lethal doses per pound killed dog B in 2 hours, while dog M survived the injection of 50 minimum lethal doses per pound. At the time of death, the animals showed a tendency to bleed from the incision employed when the femoral vessels were exposed; gingivae and nostrils. The liver was congested and a hemolytic exudate had collected in the peritoneal cavity.

Hemolysis was a constant finding in the fatal cases. In a few dogs (P, D, V) hemolysis was already present in samples taken immediately after the injection of toxin was completed; in others (J, L, N, O, Q) the onset was delayed. Absence of hemolysis was the rule in dogs that survived, exceptions being dogs K and D (slight hemolysis and no death) and dog S (no hemolysis and death).

The blood glucose level did not change significantly during the injection or after it was completed. However, in the dogs that died, samples taken shortly before death (5 to 10 minutes) showed either a marked hypoglycemia (dogs J, Q, V) or hyperglycemia (dogs N, O, P). A reduction in the lipoid content of the adrenal cortex fasciculata and reticularis layers accompanied these changes in the blood glucose level, being specially marked in the hypoglycemic cases.

The prothrombin concentration of plasma was always decreased near the time of death, and reached hemorrhagic levels in 2 cases (dogs O, V, Fig. 10). The histological picture of the liver always showed acute congestions, dilatation of the sinusoids and, in the most severe cases (i.e., those characterized by a marked hypoglycemia and hypoprothrombinemia) acute necrosis and hemorrhagic infarcts (Fig. 11).

The pathological picture and blood changes here described almost duplicate those observed in the dogs which died after ligation of the hepatic proper arteries. This fact, reinforced by the findings enumerated above, give us reason to believe that lecithinase played a very important role as a lethal agent in both instances. We have seen examples of resistance to death with the intravenous injection of toxin as well as to the deprivation of the arterial supply to the liver.

We investigated the antilecithinase activity of dog serum in an attempt to explain this resistance. The blood serum of normal dogs has an antilecithinase activity which varies quantitatively from dog to dog.

Antilecithinase activity of serum. The antilecithinase activity of serum is a measure of its ability to inhibit the lecithovitellin reaction. The determination was carried along these lines: decreasing amounts of serum were left in contact with a fixed amount of Clostridium perfringens alpha-toxin for a definite period of time, after which the remaining lecithinase activity was measured on aliquots of the mixture by the lecithovitellin reaction. The antilecithinase activity was expressed by the number of toxin units that had been inhibited by 1 milliliter of serum. The toxin was freshly diluted with sterile saline so as to contain 50 minimum lethal doses per milliliter. One milliliter of this dilution was measured in each of a series of tubes. To these was added 1 milliliter of decreasing serial dilutions of serum made up with sterile saline. The control tube was prepared with 1 milliliter of toxin dilution plus 1 milliliter of saline. After mixing, the tubes were left standing for 30 minutes at room temperature. A 0.2 milliliter aliquot was then taken from each tube and the lecithinase activity determined by the lecithovitellin reaction as follows: the number of units found in the aliquot, multiplied by 10, was deducted from 50 (i.e., the original amount of toxin units) and referred to 1 milliliter of serum by means of the dilution factor.

Lecithinase activity. Lecithinase activity of samples was determined on the basis of work done by Van Heyningen and by McLean (26). The borate-boric acid solution recommended by McLean was used as a buffer and a calcium ions source. The lecithovitellin substrate was prepared according to the method of Owen and associates; merthiolate was added to the final product to a concentration of 1:10,000. The antitoxin was a polyvalent one, containing 10,000 units of Clostridium perfringens

TABLE VI.—INTRAVENOUS INJECTION OF ALPHA TOXIN

	Sex Weight lbs.	Toxin units per lb.	Glucose gm. per cent	Hemolysis	Prothrombin	Remarks
Dog B	F.	8.0				Died 2 hours after injection
Before injection	25		0.75			
After half dose			0.83			
At end			0.64			
Dog C	M.	7.0				
Before injection	27		0.93			Survived
After half dose			0.89			
At end			0.93			
Dog D	F.	7.0				
Before injection	27		0.86	—		Survived
After half dose			1.08	+		
At end			0.96	++		
Dog E	F.	10.0				Survived
Before injection	20		0.77			
After half dose			1.09			
At end			1.27			
Dog F	F.	8.0				Survived
Before injection	25		0.65			
After half dose			1.04			
At end			1.20			
Dog G	F.	20				Survived
Before injection	20		0.75	—		
After half dose			0.82	—		
At end			0.78	—		
Dog H	F.	20				Survived
Before injection	20		0.75	—		
After half dose			0.87	—		
At end			0.81	—		
Dog I	M.	30				Died overnight
Before injection	20		0.73	—		
After half dose			0.76	+		
At end			0.75	++		
Dog J	F.	40				Died while drawing last sample
Before injection	15		0.75	—	77.7	
At end			0.78	—	80.4	
3 hours after			0.63	+++	75.4	
3½ hours after			0.27	++++	54.1	
Dog K	F.	30				Survived
Before injection	20		0.82	—	84.0	
At end			0.89	—	92.2	
4 hours after			0.84	+	80.4	
6 hours after			0.82	—	96.4	
Dog L	F.	40				Died overnight
Before injection	22		0.75	—	77.7	
At end			0.73	—	83.0	
4 hours after			0.77	++++	51.4	
8 hours after			0.70	++	—	
Dog M	F.	50				Survived
Before injection	19		0.79		88.7	
At end			0.87		89.5	
4½ hours after			0.82		98.7	
Dog N	M.	75				Died 5 minutes after drawing last sample. Hemolytic fluid in abdomen
Before injection	20		0.89	—	113	
At end			0.67	—	98.7	
2½ hours after			2.90	++++	44.4	
Dog O	F.	75				Died while drawing last sample. Hemolytic fluid in abdominal cavity
Before injection	15		0.80	—	89.5	
At end			0.83	—	91.4	
3 hours after			3.10	+++	13.0	
Dog P	M.	60				Died while drawing last sample. Hemolytic fluid in abdominal cavity
Before injection	25		0.75	—	87.7	
At end			1.00	+	95.6	
2 hours after			2.88	++++	46.0	
Dog Q	F.	40				Died immediately after drawing the sample
Before injection	20		0.79	—	92.2	
At end			0.90	—	81.3	
2½ hours after			0.28	++++	51.7	
Dog S	M.	33.3				Died overnight
Before injection	15		0.85	—	84.0	
At end			0.83	—	78.7	
7½ hours after			0.89	—	58.4	
Dog V	M.	50				Died after drawing last sample. Hemolytic fluid in abdomen
Before injection	15		0.78	—	92.9	
At end			0.92	+++	85.8	
3 hours after			0.37	++++	17.8	

antitoxin; it was freshly diluted 1:40 with sterile saline for use. Two tubes were set for each determination; 0.5 milliliter of buffer solution was measured in each, followed by the required amount of sterile saline. One milliliter of antitoxin dilution was next added to tube 2. The desired amount of sample was then pipetted into both tubes and after being mixed by rotation, these were allowed to stand for 2 or 3 minutes. Finally, 1 milliliter of the lecithin-vitellin substrate was added and the tubes were incubated in a water bath at 37 degrees centigrade for 30 minutes. At the end of this period 1 milliliter of antitoxin dilution was run into tube 1 and both tubes were cooled in cold water. The final volume of the mixture was 7 milliliters, the amount of saline to be added varying according to that of the sample used since the volume of buffer solution, lecithovitellin substrate, and antitoxin dilution was kept constant. For the turbidimetric readings a model 14 Coleman spectrophotometer was used, set at 660 micro mu. The transmittance values were converted to minimum lethal dose by reference to a standard curve obtained with toxin and checked for every set of determinations. The lecithinase activity was expressed as minimum lethal dose. Antilecithinase activity was determined on the serum of (1) dogs submitted to the intravenous injection of toxin and (2) dogs with ligated hepatic arteries. Typical examples are shown in Table VII.

In the present experiments the toxin used was a filtrate from a BP6K strain culture (Bull and Pritchett culture, 15) whose origin is somewhat obscure. This strain produces a toxin particularly rich in alpha factor, i.e., high lecithinase activity. When this toxin was given intravenously to normal dogs, in doses which did not produce hemolysis, the determination of the antilecithinase activity of blood serum could be carried out.

As it can be seen in Table VII, in the case of dog B, the antilecithinase activity of blood serum dropped to 0 after the injection of toxin was completed and the animal died 2 hours later. On the other hand in the surviving dogs C and G the initial drop was followed by an increase of the ability of their sera to inhibit Clostridium perfringens lecithinase. Determinations were also carried out on the blood serum of dogs with ligated hepatic proper branches but in this instance the true antilecithinase activity levels were masked by the simultaneous occurrence of hemolysis. We found that the products of the lysis of red cells inhibit the lecithovitellin reaction in vitro (39). It may be interesting, though, to mention the fact that the survival of two of these dogs was coincidental with an increased inhibitory activity of the corresponding unhemolyzed sera.

TABLE VII.—ANTILECITHINASE ACTIVITY OF SERUM OF DOGS INJECTED WITH ALPHA TOXIN

	Toxin units per pound	Toxin units inhibited by 1 ml. of serum	Hemolysis	Remarks
Dog B				
Before injection	8	48.0	—	Died 2 hrs. after injection
After injection		0.0	—	
Dog C				
Before injection	7	66.0	—	Survived
After injection		25.0	—	
5 days after		86.0	—	
Dog G				
Before injection	20	132.0	—	Survived
After injection		96.0	—	
24 hrs. after		118.0	—	

On the basis of these results, we contemplated the possibility of counteracting the lethal effects of the hepatic artery ligation in dogs by previously immunizing them against the alpha-toxin of Clostridium perfringens. Three dogs were periodically injected, by the intravenous route, with increasing amounts of Clostridium perfringens, type A, toxic filtrate, and the antilecithinase activity of the serum was correspondingly recorded. When 1 milliliter of serum inhibited between 1.320 and 2.700 minimum lethal doses, the dogs were submitted to the ligation of the hepatic proper branches as described before. All animals died within 4 to 5 days after surgery. These results show that some protection had been obtained in the "vaccinated" dogs, since the survival period was prolonged. In previous studies, it was found that dogs which had recovered from experimental appendicitis had an enhanced antilecithinase activity of blood serum. The serum was more effective in preventing the lecithovitellin reaction performed

with sac fluid (36) than commercial polyvalent antitoxin. The serum was also as effective as the commercial polyvalent antitoxin in inhibiting the lecithovitellin reaction of Clostridium perfringens type A toxic filtrate. It was then concluded that the "inability of commercial gas gangrene antitoxin to neutralize the lecithinase activity found in the exudates analyzed and the high degree of inhibition from serum of convalescent dogs was due to the likelihood that the anaerobic organisms harbored by the dog are of a different species than those in man." Wolbach and Saiki found an anaerobic spore-bearing bacterium in the livers of 21 of 23 healthy dogs. Berg, Zau, and Zobling found in the livers of 3 of 11 dogs an anaerobic identified as Bacillus welchii. In the others, they found an unidentified anaerobic spore-bearing bacterium. Most of the workers in this particular field agree that the anaerobe found in the livers of dogs is not Bacillus welchii (6).

It can be assumed that if a production of toxin by the proliferating bacteria in the liver, which was deprived of its arterial supply, is sustained, then the antilecithinase activity increased by the previous intravenous injections of alphatoxin will be easily overcome. No conclusion is warranted, however, since it is not known how specifically the increased antilecithinase activity of serum against Clostridium perfringens toxin will act on a toxin produced by clostridia growing in the liver of dogs. As a matter of fact, a high antilecithinase activity of serum does not appear to be the protective mechanism which has to do with "resistance." One fact remains, however, i.e., no matter how high the antilecithinase can be increased, it will not prevent the growth of bacteria.

Penicillin treatment. In Table VIII are shown the results of 5 dogs which were treated daily with 300,000 units of penicillin intramuscularly for 4 consecutive days after the ligation of all the hepatic proper branches of the hepatic artery. It is clearly shown that death was prevented.

Slight variations in the prothrombinemia was observed after surgery. Variations in the alkaline phosphatase also was found and 3 dogs (dogs 2, 3, 6) revealed a maximum level between 48 and 72 hours following the operation. After 72 hours a decline began which reached the normal level at the end of a 50 day period.

We interpreted the variation in phosphatasemia as due to the cholecystectomy which was always performed at the time of the operation. Hemolysis was never observed.

DISCUSSION

Haberer established three criteria in order to remove many of the pitfalls in this type of investigation. They are as follows: (1) The point of ligation should be accurately stated. (2) The experiments should be terminated with arterial injections in order to establish the existence of collateral circulation. (3) The operation should be done aseptically.

We have fulfilled all these requirements. A high percentage of dogs operated upon and without penicillin after operation died. Our results show that acute ligation of the hepatic proper arteries produced a mortality of 68.7 per cent. Death may occur during a period which varies from 17 hours to 4 days. The average time of survival was 37 hours. A group of dogs (31.3 per cent) survived the operation and in these no arterial collateral circulation was found to account for their survival. The small vessels which occasionally remained patent and coursed in the hepatoduodenal ligament, derived from small branches of the posterior superior pancreaticoduodenal artery, will not carry enough arterial blood to the liver to account for the survival of the dogs. Dogs were found to survive even without having these small vessels present in the hepatoduodenal ligament.

Livierato and associates pointed out that small arterioles, derived from the inferior phrenic artery, coursed along the hepatic veins as the latter vessels leave the liver to join the inferior vena cava. In their experiments, they ligated the inferior phrenic arteries in order to prevent this occurrence of this collateral circulation. Haberer also pointed out this collateral circulation pathway as a possibility. Huggins and Post presented a specimen that revealed this same circulatory pathway when the ligation of the hepatic proper branches was done in stages.

TABLE VIII.—LIGATION AND SECTION OF LIVER BRANCHES OF HEPATIC ARTERY, RIGHT GASTRIC ARTERY AND CHOLECYSTECTOMY—(PENICILLIN, 300,000 UNITS, INTRAMUSCULARLY DAILY DURING 4 DAYS AFTER SURGERY)

	Sex	Weight mgm.	Hematocrit per cent	Glucose per cent	Proteins per cent	Alkaline phosphatase	Prothrombin per cent	Remarks
1	F.	10.4						Sacrificed
Before surgery			45.0	0.69	5.41	1.24	66.6	
24 hrs. after surgery			45.5	0.96	5.3	2.53	48.7	
48 hrs. after surgery			43.0	0.91	5.6	2.64	81.5	
72 hrs. after surgery			38.4	0.87	5.45	1.87	77.0	
11 days after surgery			39.1	0.68	5.1	6.6	68.2	
30 days after surgery			44.8	0.87	5.3	0.98	—	
43 days after surgery			44.4	0.77	5.4	0.85	69.5	
2	M.	6.7						Sacrificed
Before surgery			54.6	0.70	6.3	1.45	54.3	
24 hrs. after surgery			54.1	0.75	6.1	7.20	52.8	
48 hrs. after surgery			47.5	0.85	5.6	5.73	55.5	
72 hrs. after surgery			46.5	0.89	5.8	16.7	59.7	
10 days after surgery			44.9	0.81	6.1	15.6	81.5	
29 days after surgery			52.6	0.74	6.1	11.5	—	
42 days after surgery			54.5	0.69	6.1	9.2	76.6	
3	F.	14.5						Sacrificed
Before surgery			57.0	0.87	6.1	2.46	71.4	
24 hrs. after surgery			57.5	0.92	5.8	5.30	65.0	
48 hrs. after surgery			55.5	0.95	5.6	10.3	86.4	
72 hrs. after surgery			53.9	0.80	5.5	11.5	80.6	
9 days after surgery			52.7	0.82	6.1	7.1	114.0	
37 days after surgery			63.0	0.70	6.1	1.9	50.0	
5	M.	11.3						Sacrificed
Before surgery			53.8	0.80	5.9	1.34	86.2	
48 hrs. after surgery			55.1	0.96	5.6	12.4	73.5	
29 days after surgery			48.4	0.79	5.3	17.9	57.4	
51 days after surgery			51.0	0.82	5.8	14.6	± 100.0	
6	M.	9						Sacrificed
Before surgery			37.0	0.83	6.7	0.94	73.6	
48 hrs. after surgery			35.1	0.90	6.2	10.9	62.1	
29 days after surgery			35.1	0.89	6.8	4.1	45.0	
51 days after surgery			38.1	0.89	7.1	1.24	± 100.0	

We have not been able to demonstrate the above avenue for collateral circulation in studies on normal dogs and in the dogs that have spontaneously survived the acute ligation of the hepatic branches. The only time we were able to see branches of the inferior phrenic arteries coursing along the inferior surface of the diaphragm was when we injected the celiac axis or the abdominal aorta.

In order to determine how far the material injected in the hepatic artery would pass into the liver, we examined frozen sections of the liver which were taken from its superior surface. The red-lead material was found in close proximity to Glisson's capsule but no material was found immediately under the capsule. As we have pointed out in the anatomical studies, injection of the hepatic proper arteries in dogs failed to demonstrate a subcapsular network of anastomosis beneath Glisson's capsule, and also any connection with the inferior phrenic arteries in the coronary and falciform ligaments, in the event that the latter ligament was present.

One exception to this statement was found in a penicillin treated dog which deserves a special comment. This dog was sacrificed 2 months after surgery. The anatomical study revealed that the red-lead material injected into the common hepatic artery gained entrance to the inferior phrenic arteries. When injected into the common hepatic artery the dye passed into the posterior superior pancreaticoduodenal artery which anastomosed with the inferior pancreaticoduodenal artery. Through this latter vessel the dye coursed through the proximal portion of the common hepatic artery which in turn originated from the celiac axis. In this specimen, both inferior phrenic arteries originated from the celiac axis. Small branches from the right inferior phrenic artery were seen in the areolar tissue between the right crus of the diaphragm and the inferior surface of the liver. As the right inferior phrenic artery coursed on the diaphragm near its dome, small branches were seen to leave the left inferior phrenic artery as it ascended on the diaphragm and the former vessels

coursed in the left coronary ligament to the liver's edge of the left lobe. As this branching of the inferior phrenic arteries was never observed in normal dogs or in those that were sacrificed before 2 months after operation, we assume that the development of these small collateral vessels derived from the inferior phrenic arteries, occur slowly and as a result of a not well understood vascular compensatory mechanism. It may be possible that these vessels are a part of natural collateral circulation which comes into use only when the demands of the organ are great. We consider that the demands of the organ for arterial blood are great when its main arterial supply is abolished, since we have observed that when the hepatic proper branches were ligated, but not transected, a recanalization of these arteries occurred in the late postoperative period.

In some instances, due to a break of continuity of the posterior superior pancreaticoduodenal artery, this vessel had to be ligated. This procedure might be considered a contributing cause of death; however, we do not believe that the ligation of the posterior superior pancreaticoduodenal artery alters the outcome of the animal in any way. Our contention is that the inferior pancreaticoduodenal artery will be a source of natural circulation to the area deprived of its arterial supply by ligation of the superior pancreaticoduodenal artery.

Cholecystectomy does not influence the final outcome (death or survival after ligation of the hepatic proper arteries) of the animals. However, the presence or the absence of the gall bladder bears a close relationship to the change of the alkaline phosphatase in the blood as will be discussed later.

The results obtained when the dogs were treated with penicillin revealed two facts:

1. That perforation of the gall bladder could be the cause of death (by peritonitis). A congested gall bladder was always observed in dogs operated upon by Huggins and Post. Even those which survived after ligation of the hepatic artery in stages presented this latter finding.

2. The recanalization of the hepatic proper branches observed in the late postoperative period, when the branches were ligated but not severed, cannot be considered a pitfall since the nontreated dogs in which the same operative procedure was used died. A matter of conjecture then arises as to what moment of the postoperative period the recanalization takes place. When the branches were ligated and severed, no revascularization was observed. The "call" for a collateral circulation may be great and an expression of it might be the small vessels observed in the hepatoduodenal ligament and the exceptional case in which the inferior phrenic arteries gave off small branches to the liver. All these vessels together will give only a minimal arterial supply to the liver and will not explain the survival of the animal. Dogs that had ligation and transection of the hepatic branches, but received no penicillin postoperatively, also survived. No collateral circulation in these animals was demonstrated. When a penicillin treated dog died because of perforation of the gall bladder, the animal survived a period long enough to warrant consideration that the liver parenchyma itself was withstanding fairly well the lack of arterial supply. In our study, variation of branching of the hepatic artery was not encountered. In only one instance did the right gastric artery originate from a hepatic proper branch, distal to the ligature and point of transection, instead of from its usual origin, the common hepatic artery.

The fact that penicillin prevented death suggests that a factor which is not specifically related to the arterial supply of the liver cells, is involved in the cause of death. The blood changes found in the series of experiments reflected a profound alteration which took place in the liver when ligation of the liver branches of the hepatic artery was followed by death. A remarkable observation was that this change was of a very rapid nature when the blood alteration obtained 3 hours before death was compared with the alteration found at the time of death. This result gives more support to the conclusion reached in a previous experimental study of liver function tests (40); i.e. that prothrombinemia and phosphatasemia become more abnormal as the severity of the hepatic damage increases and that it is more

reasonable to accept the concept of quantitative association of the liver function tests than of qualitative dissociation of the liver's function.

The behavior of the alkaline phosphatase deserves comment. In general, our experiments revealed the highest level of alkaline phosphatase activity in dogs which did not survive. The results seen in the penicillin treated dogs permits us to state, with some certainty, the quantity of liver damage produced by the ligation of the hepatic proper branches per se. There are three possibilities that must be considered when interpreting the changes of the alkaline phosphatase activity. They are as follows:

1. Cholecystectomy alone will cause an increase in the alkaline phosphatase activity by producing a dilatation of the bile ducts and incompentency of the sphincter of Oddi which in turn permits transmission of the intraduodenal pressure into the biliary tract.

2. A change in the intrahepatic biliary pressure may produce an increase in the alkaline phosphatase activity; in our operative technique some traction on the common bile duct was made, consequently, edema and a slight inflammatory reaction due to this mechanical traction may occur and thus cause increased intrahepatic biliary pressure.

3. By severing the arterial supply to the liver and consequently the supply to the intrahepatic ducts, pathological changes take place which may alter the histological structure of the biliary canaliculi.

In our experiments the above three possibilities existed. Therefore, the amount of change of the alkaline phosphatase activity found cannot be related either to hepatocellular damage, or to extra hepatic or intrahepatic biliary changes alone. As significant differences in the activity were not observed when cholecystectomized and noncholecystectomized dogs were compared, apparently the changes in the alkaline phosphatase activity are of some prognostic value. Furthermore, the highest figures were observed in the dogs which died regardless of the fact of whether or not the gall bladder was removed. Therefore, we can state that the increase of alkaline phosphatase activity reflects a profound alteration in the structure of the entire hepatic unit. In fact, icteric plasma was observed at the time of death. In penicillin treated dogs some increase of the alkaline phosphatase activity was found as can be seen in Table VIII. These variations we interpret as due to the cholecystectomy and to unavoidable traction on the biliary structures during surgery.

When hepatic damage is so profound as to produce an alteration in the carbohydrate metabolism, it can be assumed that total liver insufficiency has been obtained, as in total hepatectomy, and death will ensue. The fact that many of the symptoms and blood changes observed after ligation of the arterial supply to the liver are similar to those observed after total hepatectomy, may lead one to the conclusion that lack of the arterial supply to the liver produces total liver insufficiency. Our experimental result, however, shows this to be not true since survival was observed in dogs with mild blood changes and in which anatomical studies demonstrated no arterial supply was left intact. In the penicillin treated dogs the blood changes were as slight as those found in the dogs which survived without treatment and it may be assumed then, that deprivation of the arterial supply to the liver per se is not the cause of death.

Hemoconcentration was always found at the time of death with hemolysis as a constant companion, although these findings were never found in the penicillin treated dogs. When these findings are compared with the hemodilution and lack of hemolysis found in the dogs which survived, the two findings are very remarkable. Hemoconcentration could be explained by excessive fluid loss, an example of which is the constant presence of hemolytic fluid in the peritoneal cavity at the time of death. However, the usual presence of hemolysis in plasma cannot be explained by excessive loss of fluid.

We have observed most of the histological changes, as described in the literature, in the liver of the dogs that died. Dogs sacrificed in the morbid state revealed bacteria, having the characteristic of anaerobic rods, occupying the vessels and the intracellular spaces. These findings demonstrated that proliferation of bacteria had taken place in the liver. If the

bacteria did not originate in the liver, then it must be assumed that normally the liver has a bactericidal function which is altered when the liver is deprived of arterial blood. In the penicillin treated dogs no histological changes in the liver were observed except a slight cloudy swelling.

On the other hand, in some instances death could not be explained on the liver histology. The histological criteria adopted, on which is based the degree of the hepatic injury, were the status of the nuclei and the number of unaltered cells in the hepatic unit. We would emphasize the fact that most of the changes described were seen in the same liver and that the regenerative capacity of the organ could be determined only by the number of unaltered cells or the number of cells remaining with normal nuclei, as no regenerative changes were observed around the infarcts of the dogs that died. This concept is compatible with the profound alterations found in the blood at the time of death.

Since the liver has a dual blood supply, the interpretation of the histological findings cannot be accurate if one considers the picture only from a circulatory standpoint. It is known that there is a reciprocal response between the flow in the hepatic artery and the portal vein (21). If the flow increases or decreases in one, it does the opposite in the other vessel. It is also known that arterial terminals empty directly into the sinusoids and most of the sinusoids contain blood from both sources (43). Therefore, it is difficult to accept the histological changes described by us as being due exclusively to the lack of arterial blood.

We consider that the dog's liver can survive the loss of its arterial supply and that another important factor must be sought for the cause of death besides ligation of the hepatic branches per se. The factor which appeared to play the most important role in the cause of death was lecithinase, since lecithinase was found in the abdominal fluid of dogs that died. This lecithin-splitting enzyme is considered the main lethal factor and has been identified with the alpha-toxin of Clostridium perfringens, type A, organisms whose properties appear to correlate well with their ability to produce this toxin. The injection of alpha-toxin intravenously in the dog reproduced, in our hands, the same pathological picture and blood changes followed by death which we have observed in the dogs which died from ligation of the hepatic proper branches. Hemolysis was a constant finding in the fatal cases, by either method, and absence of hemolysis was the rule in the dogs that survived. The prothrombin concentration of plasma was always decreased near the time of death and reached hemorrhagic levels in 2 cases. In dogs that died, samples taken shortly before death revealed either a marked hypoglycemia or hyperglycemia. The histological picture of the liver always showed changes of acute congestion, dilatation of sinusoids, and in the most severe cases (i.e. those characterized by marked hypoglycemia and hypoprothrombinemia) acute necrosis and hemorrhagic infarcts.

One fact deserves special comment. Dogs receiving the toxin, as well as those in which ligation of the liver branches of the hepatic artery was done, showed a reduction of the lipoid content of the adrenal cortex fasiculata and reticularis layers which accompanied the changes in the blood glucose level, being specially marked in the hypoglycemic cases (Figs. 10 and 12).

It is known that death follows adrenalectomy in dogs and that hypoglycemia is a constant finding. Since the adrenal cortex is a tissue which is very rich in lipoids, the lecithin-splitting action of lecithinase may be responsible for the depletion of lipoids and the structural changes found. Death could be interpreted on this basis. The hypoglycemia might not be the only result of a depleted cortex, since in both instances liver injury was also present. Since it has been shown that injections of adrenal cortex extracts increase the resistance of rats to death against alpha-toxin (42), one wonders if cortical steroids related with carbohydrate metabolism will protect the liver and increase the resistance through glycogen storage in the liver. The depletion of sudanophilic material of the adrenal cortex found in dogs submitted to ligation of the hepatic proper arteries cannot be considered a direct consequence of the lack of arterial blood to the liver but of lecithinase originating from anaerobic bacteria in the liver. Hence, if the

liver has a bactericidal function, a liver-adrenal cortex homeostatic mechanism seems important, a hypothesis which deserves further investigation.

There was a 31.3 per cent survival rate in our series of dogs which were operated upon but received no penicillin treatment. No collateral circulation to the liver was found to account for their spontaneous recovery. Markowitz and associates (22b) recently reported that "the immediate urgent function of the hepatic artery is to keep the oxygen tension of the liver sufficiently high to discourage proliferation of anaerobic bacteria." The liver is able to utilize oxygen from the blood of the portal vein (13, 38) and the spontaneous survival of the nontreated dogs in our series might be the result of a well adjusted mechanism in these animals through which enough oxygenated blood was carried by the portal blood. Huggins and Post, however, found that oxygen determinations on the blood of the portal and hepatic veins revealed that a further reduction of portal blood occurred in the liver of dogs when ligation of the hepatic artery was performed in stages. We have carried out a few experiments which agreed with the results of Huggins and Post. The blood clearance of intravenously injected radioactive fluorescein by the liver, was markedly delayed in the penicillin treated dogs 2 months after the ligation of the hepatic proper branches. If these preliminary results are to be interpreted as a consequence of a reduced blood flow in the liver deprived of its arterial supply, other factors besides oxygen tension may be equally important in accounting for the survivals.

The presence of lecithinase in the abdominal fluid of the dogs dying after ligation of the hepatic proper arteries, and the observation that the same symptoms, blood changes, and death are reduplicated by the intravenous injection of alpha-toxin in normal dogs, gives support to the belief that lethal enzyme production by anaerobic bacteria is carried on in the liver deprived of its arterial supply. Death which follows is thus due to the metabolic disturbances produced by the action of the invading enzymes on the host tissues.

Our attempt to prevent the death of dogs with ligated hepatic proper arteries by active immunization against Clostridium welchii alpha-toxin previous to the ligation failed. However, a prolonged period of survival was obtained with this treatment, and the average time of survival was increased from 37 to 98 hours. The lecithinase-antilecithinase ratio could not be determined in the dying dogs because of the constant presence of hemolysis in their blood serum, thus interfering with the lecithovitellin reaction. The presence of hemolysis revealed the fact that lethal enzyme production had overcome the "protection" afforded by a high antilecithinase activity of serum. As a matter of fact, a high antilecithinase activity of serum will not prevent the growth of bacteria in the liver.

It is logical to assume that penicillin inhibits the growth, or proliferation, of the anaerobic bacteria in the liver, thus preventing the lethal enzyme production. As for the results in the animals which received no penicillin and survived, it would appear to us that the resistance of the liver against proliferation of anaerobic bacteria is related to other "unknown" factors besides the oxygen tension of the remaining liver blood supply. In fact, in our experience the rate of survivals in the nonpenicillin treated dogs varied according to the season in which these animals were operated upon. On the other hand does the presence of living anaerobic bacilli in the liver of dogs which die mean that the liver destroys them in those dogs which spontaneously survive? If so, the seasonal variations and bactericidal function of the liver may well be factors to be considered in explaining the spontaneous recovery of the nontreated dogs.

SUMMARY AND CONCLUSIONS

1. Ligation of the liver branches of the hepatic artery (hepatic proper arteries) in 32 dogs produced a mortality of 68.7 per cent. The death may occur in a period ranging from 17 hours to 4 days. The average time of survival was 37 hours.

2. Ten dogs (31.3 per cent) survived operation and in these no arterial collateral circulation was found to account for survival.

3. Treatment with penicillin in doses of 300,000 units daily for 4 days postoperatively prevented death in 8 dogs (100 per cent).

4. Anatomical studies performed with the injection of red lead material in the hepatic proper arteries in normal dogs failed to demonstrate a subcapsular anastomosis beneath Glisson's capsule and any connection with the inferior phrenic arteries in the coronary and falciform ligament, if the latter ligament is present.

5. Treated and nontreated dogs were sacrificed at various periods during their postoperative course. The time interval after operation was great enough so that one could assume that these animals would survive indefinitely. It was found that when the hepatic proper arteries were ligated but not severed, recanalization occurred within 2 months after operation. When the hepatic proper branches were ligated and severed, the postoperative anatomical studies revealed that small vessels, derived from the posterior superior pancreaticoduodenal artery, remained patent and coursed in the hepatoduodenal ligament to the hilus of the liver. These vessels will not carry enough arterial blood to the liver to account for the survival of the dogs. Dogs were found to survive even without having these small vessels present in the hepatoduodenal ligament.

6. Cholecystectomy does not influence the final outcome of the animals. However, the presence or absence of the gall bladder bears a close relationship with the change of the alkaline phosphatase in the blood. In the noncholecystectomized dogs treated with penicillin, perforation of the gall bladder can occur and cause death by bile peritonitis.

7. In the nontreated dogs which died, profound alterations which take place in the liver and in other tissues are reflected by the severe hypoprothrombinemia, hyperphosphatasemia, hypoglycemia, hemolysis, hemoconcentration, and histological changes in the liver and adrenal cortex. These changes are of a very rapid nature, as is shown when the blood alterations obtained 3 hours before death were compared with the alterations found at the time of death. The fact that many of the symptoms and blood changes observed after ligation of the arterial supply to the liver are similar to those observed after total hepatectomy may lead one to the conclusion that lack of arterial supply to the liver produces a total liver insufficiency. Our experimental results, however, show this to be not true since survival was observed in dogs in which anatomical studies demonstrated that no arterial supply remained intact.

8. The fact that penicillin prevented death suggests that a factor which is not specifically related to the arterial supply of the liver cells is involved in the cause of death.

9. Dogs sacrificed in the morbid state revealed bacteria in the liver, having the characteristics of anaerobic rods, which occupied the vessels and the intercellular spaces. In the penicillin treated dogs no histological changes were observed except slight cloudy swelling. Necrosis and infarcts were the characteristic findings in the dogs which died.

10. Lecithinase was found in the abdominal fluid in the dogs which died. This lecithin-splitting enzyme is considered the main lethal factor. It is known that this enzyme has been identified with the alpha-toxin of Clostridium perfringens, type A organisms, whose properties appear to correlate well with the ability to produce this toxin. The injection of this toxin intravenously in the dog reproduced, in our hands, the pathological picture and blood changes followed by death which we have observed in the dogs which succumbed from ligation of the hepatic proper arteries. Hemolysis was a constant finding in the fatal cases in both instances and absence of hemolysis was the rule in dogs which survived. Depletion of the lipoids of the adrenal cortex was observed in both instances and hypoglycemia cannot be interpreted only as the result of the depleted cortex since liver injury was always present. A liver-adrenal cortex homeostasis seems important to account for a bactericidal function of the liver.

11. By means of active immunization against Clostridium welchii alpha-toxin previous to the ligation, the average hours of survival were increased from 37 to 98 hours.

12. The dog's liver can survive the loss of its arterial supply. Penicillin prevents death by inhibiting the growth, or proliferation, of the anaerobic bacteria and lethal enzyme production in the liver. In explaining the spontaneous recovery of nontreated dogs, factors

such as seasonal variation in resistance and bactericidal function of the liver, must be considered.

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RICHTER'S HERNIA

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RICHTER'S hernia is a relatively uncommon type of hernia which was established as a clinical entity by Richter in 1778. Even though it bears Richter's name, the hernia was described by Fabricius Hildanus in 1598. Cattell reported that Littré in 1700 described 3 cases of hernia in which only a portion of the bowel wall was found within the sac. Two of these cases were later recognized as involving Meckel's diverticulum but the third was not well delineated. It was not until 1815 that Meckel described the structure which now bears his name, thus clarifying the true nature of the first two cases of Littré. Foltz described this type of hernia as a protrusion of a portion of the circumference of the intestine, usually the antimesenteric border, through a hernial ring.

Even today, confusion exists as to exactly what constitutes a Richter's hernia and what a Littré's hernia. Since a definition of the former has already been given, it must follow, from his original cases, that a Littré's hernia involves protrusion of a Meckel's diverticulum through a hernial ring. This differentiation was clearly established by Treves in 1887, at which time he was able to glean from the literature 53 true Richter's hernias out of the 80 cases which had been reported at that time. Governale and his associates, in 1941, collected and compiled 63 more cases and added 1 of their own, making a total of 117 to that date. Of these last 63 cases, all were femoral and all true Richter's hernias. Since that time, Foltz has collected 6 more and reported 3 himself.

According to Foltz, 90 per cent of Richter's hernias or partial enteroceles are femoral, the right femoral canal being more frequently involved than the left. Next in order of frequency of occurrence are the inguinal, umbilical, obturator, epigastric, and abdominal hernias. But only 0.7 of 1 per cent of femoral hernias are true partial enteroceles. The incidence as regards sex is about 3 to 1 with the majority occurring in the female.

Foltz has tabulated the following requirements for the development of a Richter's hernia: (a) the presence of a hernial sac; (b) a ring small enough to prevent engagement of the entire loop of bowel; (c) a hernial ring tight and unyielding at the time of increased abdominal pressure which forces a portion of the bowel wall through the ring in the form of a diverticulum; (d) strangulation or incarceration is always present.

In view of the clinical picture presented by many patients with this condition, it is believed that possibly there may be another explanation of the mode of development of these lesions. The fact that many patients present themselves with a history suggestive of either transitory complete or partial small bowel obstruction, followed by subsidence of obstructive symptoms has led to the following hypothesis: with an increase of intra-abdominal pressure, a loop of small gut engages the hernial ring and enters the sac, following which edema of the involved loop develops, resulting in incarceration. Very soon, symptoms of mechanical small gut obstruction ensue. The propulsive efforts of the distended bowel result in partial reduction of the contents of the sac, with re-establishment of continuity of the intestinal lumen, leaving an antimesenteric segment of bowel caught in the ring, since its swelling has continued to progress during the development of the hyperperistalsis and partial reduction. Such an etiological concept explains the history of one of the cases to be presented later.

Usually after such a hernia has been strangulated 48 hours, gangrene ensues. This is followed very frequently by death from peritonitis and paralytic ileus, or perforation through the soft parts to the exterior with enteral fistulization.

In symptomatology and diagnosis lies the real problem presented in partial enterocele.

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There is no constancy to the clinical picture. Usually with the onset there are symptoms of intestinal obstruction with cramping, colic-like abdominal pain, nausea, and vomiting. These, however, may be mild and transient. The vomiting is often intermittent and rarely fecal. Constipation is common but flatus may be passed. Mucoid stools or melena are rare. The presence of a protruding mass in any area replete with hernia potential should lead one to suspect the diagnosis. Occasionally obstructive symptoms will subside but those of gangrenous bowel may persist, such as fever, tachycardia, and leucocytosis. Sometimes a mass cannot be palpated but often there may be tenderness over the involved hernial site on manual pressure. The diagnosis obviously is extremely difficult under these conditions and Governale reports that in only 50 per cent of total reported cases up to 1941 were there symptoms of intestinal obstruction associated with a palpable mass over the suspected hernial site. A diagnosis is rarely made preoperatively due to such inconstancy of symptoms and signs, and the relative rarity of the disease process itself. Enlarged inguinal lymph nodes may interfere with accurate diagnosis.

The treatment is obviously surgical, and the sooner instituted the better the result which may be anticipated. If the hernia can be surgically released before gangrene has occurred, the postoperative mortality and morbidity will be lower. If the portion of bowel involved is necrotic, it must be removed, nearly always by resection. Excision and transverse closure of the bowel would be a questionable procedure unless the herniated area be quite small. The procedure of invagination of the necrotic portion is open also to question since the lumen of the gut would be reduced. Whenever there is any doubt as to the procedure of choice, resection and end-to-end anastomosis of the intestine is the most satisfactory operation. When the patient's condition is too precarious to allow such definitive procedures, a two stage operation may be done, with enterostomy proximal to the hernia as the first stage, followed later by excision of the lesion and re-establishment of continuity of the bowel.

The techniques of operation are varied. If a laparotomy is performed, which is usual, closure of the hernial ring may be effected by suturing of the shelving portion of Poupart's to Cooper's ligament intra-abdominally. In an extraperitoneal approach, Bailey recommends closure by approximation of the conjoined tendon to Cooper's ligament. Of course, the latter principle can be utilized in the repair of any inguinal hernia.

CASE REPORTS

CASE 1. Mrs. B. W., a white woman 65 years of age, Hospital No. 30040, was admitted to the surgical service in January, 1930, with a chief complaint of abdominal cramps. The onset of her illness was 3½ days previous to her admission, with epigastric, cramping pain. The pain increased in severity, and after an hour she vomited. She continued to vomit with each attempt at alimentation. She had no bowel movement following the onset of her illness.

Physical examination showed only abdominal distention with visible hyperperistalsis. No mass or hernia was palpable.

Laboratory studies showed only a mild hypochloremia. The remaining blood and urine studies were within normal limits.

The abdomen was explored the day following admission. Greatly dilated loops of small gut were found and a loop of ileum was adherent in the pelvis. In trying to free this loop, a segment of ileum was torn. Since the patient's condition was precarious, a Witzel-type of ileostomy was done through the tear, and the abdomen was closed. Postoperatively, her fever rose steadily, reaching 105.2 degrees F. and her pulse rate rose to 150. She died on her first postoperative day. Only at autopsy was a right femoral partial enterocele found. She died of an acute generalized peritonitis. This case has been recorded previously (6).

CASE 2. Mrs. G. S., Hospital No. 144065, white female 53 years of age was admitted to the surgical service in November, 1947, with a chief complaint of drainage from the right inguinal region of 6 weeks' duration.

She was in excellent health until 2 months prior to her admission, at which time she developed diffuse, cramping abdominal pain of sudden onset. The pain was not excruciating. This continued for 3 days, after which she began to vomit colorless fluid four to five times a day. On the fourth day of her illness she noted the development of a swelling in the right groin about the "size of an egg," and dark red in color. She was treated with injections of penicillin and streptomycin without dramatic results. A week following the onset of this illness, the patient was hospitalized and the inguinal mass incised and drained. Following her discharge from the hospital, the inguinal wound failed to heal and

drained a greenish yellow fluid, about 250 cubic centimeters per day, in quantity. Occasionally this drainage would have a fecal odor and gas would be expelled. The material sometimes appeared to be under pressure when discharged, the discharge being preceded by cramping abdominal pain.

This patient was a well developed, well nourished white female who was not acutely ill. Her positive physical findings were limited to the abdomen. There was an area of reddened, brawny induration in the right inguinal region, parallel to, and overlying, the inguinal ligament and extending medially to the mons pubis. It measured 20 by 5 centimeters in size, was tender, and two draining fistulas opened therefrom, lateral and superior to the symphysis pubis. The drainage was yellowish green and nonodorous at time of examination. No excoriation of the skin was noted. Several soft spots were located in the area of induration suggesting undermining of the skin and abscess formation.

Laboratory studies revealed a red blood count of 2.8 million, a white cell count of 4,465 per cubic millimeter, and hemoglobin 7.6 grams per cent. Her blood chemistry was within normal limits, and total serum proteins were 5.12 grams per cent. Culture of the sinus tracts identified Escherichia coli. Barium enema showed no evidence of colon disease. Instillation of radiopaque oil into the fistulous tracts showed communication with the small intestine. Following ingestion of oral methylene blue, the dye promptly appeared in the inguinal drainage.

Five days following her admission to this hospital, an incision and drainage of the abscesses in the right groin were done. Considerable undermining of the skin was found at that time. Since it was obvious that abdominal exploration was indicated, the patient was given in preparation succinylsulfathiazole by mouth for 5 days. Exploration revealed strangulation of a small antimesenteric portion of the small intestine, 40 centimeters from the ileocecal valve in a right femoral hernia. After freeing the hernial contents by incision of Gimbernat's ligament, a segment of bowel was resected and an end-to-end anastomosis was done. The hernia was closed intra-abdominally by suturing the inferior edge of the shelving portion of Poupart's ligament to Cooper's ligament. Her postoperative course was uneventful, and she was dismissed from the hospital asymptomatic on her eleventh postoperative day.

CASE 3. Mrs. K. R., a white housewife, 77 years of age, Hospital No. 166569, was admitted to the surgical service in February, 1949, with a chief complaint of severe, cramping, abdominal pain. This began early the day of admission and was increasing in severity. Within a few hours after the onset of pain, she began to vomit. This continued to the time of surgery. She had known that she had a hernia in the right inguinal area for 1 year.

The laboratory findings were within normal limits, except a leucocytosis of 15,500 with 82 per cent of polymorphonuclear forms. The electrocardiogram report showed sinus tachycardia. T-wave abnormalities suggested myocardial changes or digitalis effect. Flat films of the abdomen showed dilated gas-filled loops of small bowel with fluid levels. A calcified uterine fibroid was seen.

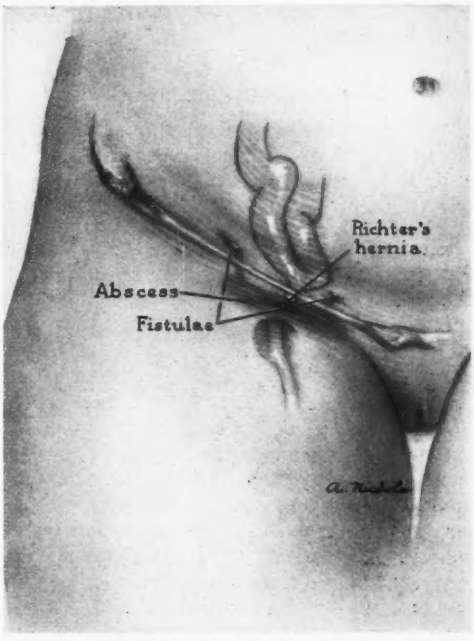

Fig. 1. Illustration showing site of perforation of a Richter's hernia through the femoral canal with external fistula formation (Case 2).

Physical examination showed an acutely ill, poorly nourished white female in great pain. Mild abdominal distention was present. There was a mass in the right groin 2.5 centimeters in diameter which was exquisitely tender. Just to the left of the midline in the lower abdomen was a firm, nontender mass 5 centimeters in diameter.

Immediately following admission a diagnosis of strangulated hernia was made, parenteral fluids administered, and gastric decompression started. She was explored the evening of her admission day and a strangulated partial enterocele of the ileum was found. The herniated portion of the bowel was gangrenous, necessitating resection. Postoperatively, her course was progressively downhill, and on her second postoperative day she had several convulsive seizures. These were clinically attributed to hypochloremia, which was confirmed by analysis. However, they persisted following parenteral correction, and the morning of her third postoperative day she developed a hypotension of 60 to 80 millimeters of mercury systolic pressure which persisted for 24 hours. She died on the afternoon of her fourth postoperative day.

The necropsy report showed generalized arteriosclerosis, subpial hemorrhage, pulmonary edema, and acute dilatation of the heart.

SUMMARY AND CONCLUSIONS

Since its original identification as a clinical entity in 1778 by Richter, 126 cases of partial enterocele have been described, including 2 cases added in this report. The vast majority of Richter's hernias are femoral in location with involvement of the right side more frequently than the left. Of all femoral hernias only 0.7 per cent are Richter's in type. Because of the statistical rarity of this condition, diagnosis is probably most often missed preoperatively because it is not considered a possibility. The symptomatology is quite vague and variable.

Therapy of the condition is discussed, and resection of bowel segment recommended when doubt exists as to its viability. Closure of the abdominal wall defect may be accomplished by the intra-abdominal or extraperitoneal route. If the former, closure of the defect may be made by evagination of peritoneum and suture of Poupart's to Cooper's ligament. If the latter, the operation to unite the conjoined tendon to Cooper's ligament is recommended.

Three cases of Richter's hernia are reviewed, one of which presented as a perforation and abscess formation in the right groin with persistent ileostomy following incision and drainage. This patient recovered promptly after operation. Two patients died, one from a cerebrovascular accident, and the other from generalized peritonitis.

The incidence of external perforation with fistulization is not known, but the possibility must be considered in the diagnosis of Richter's hernia.

A new explanation of the development of a partial enterocele is presented, which is well illustrated by Case 2.

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AN OPERATIVE APPROACH TO THE TREATMENT OF GIGANTIC HERNIAS

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GIGANTIC hernias which have forfeited their right of domicile within the peritoneal cavity have presented a most difficult problem since earliest time. Efforts at treatment have included weight reduction, rest in bed with elevation of the foot of the bed, repeated taxis, constant pressure against the hernia, repeated catharsis, massive bowel resection, and recently, repeated pneumoperitoneum preliminary to surgery. We propose an approach based upon the concept that by making a long transverse incision in the abdominal wall down to peritoneum the latter will stretch, creating space, and thus prevent undue pressure upon the diaphragm and venous systems. This operation necessarily creates a new hernia which early in its development is not severe. When the patient has adjusted himself to the newly increased abdominal contents, the artificial hernia can be repaired.

The following case illustrates the technique used in the repair of a gigantic hernia.

A 59 year old white male coal miner entered the State University of Iowa Hospitals with a history of having had an inguinal hernia since childhood which had gradually grown larger. It had reached the size of a regulation basketball. The hernia had become increasingly difficult to carry around and caused the patient to tire easily. It had never been strangulated and had been irreducible for a number of years. The patient weighed 197 pounds. Physical examination showed no abnormalities except for the massive right inguinal hernia which hung between the patient's knees and which was not reducible. The testicles were in the scrotum. Laboratory studies were normal. A roentgenogram showed extensive bowel in the hernial sac with collections of air. A barium swallow revealed a large, elongated, atonic stomach with the base of the greater curvature lying below the wing of the ilium. Five hours after the barium swallow the barium was within the bowel in the hernial sac with colon also visibly present. On May 12, 1950 the patient was operated upon. The contents of the hernial sac consisted of the entire small bowel (except for the duodenum), the omentum, and the entire colon down to the rectosigmoid junction. Under deepest anesthesia it was impossible to reduce the hernial contents into the abdominal cavity. A long transverse incision was made in the upper abdomen cutting through skin, fascia, muscles, and transversalis fascia down to the peritoneum, permitting the latter to bulge into the wound. The skin incision was then closed with a continuous subcuticular suture of No. 0000 steel wire and some interrupted No. 0000 silk. The bowel and omentum were then easily reduced into the abdominal cavity. The right testicle was removed and the internal inguinal ring was tightly closed and reinforced by imbricating the fascia. A portion of the excessive scrotal skin was excised. Postoperatively the patient had an uneventful course. Prior to the second operation, 12 days later, a nasal tube was passed into the small bowel. The abdominal incisional hernia at this operation was easily repaired by bringing the margins of the fascia together with interrupted No. 000 steel wire. The tube was removed on the second postoperative day. The postoperative period after the second operation was also satisfactory and the patient was discharged from the hospital 18 days following the second operation.

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DISCUSSION

This operation, the creation of a large abdominal incisional hernia by cutting transversely through all structures down to peritoneum and later repairing the newly created

Fig. 1. Appearance before surgery.

Fig. 2. Roentgenogram of hernial mass. Note gas in colon.

Fig. 3. Appearance after completion of surgery.

hernia, prevents the respiratory difficulty and circulatory embarrassment that so often results from replacement of a large mass of bowel into the abdominal cavity. This same procedure can be applied to massive umbilical or diaphragmatic hernias. The peritoneum will expand to house the added structures thus preventing pressure upon the diaphragm and, what is even more important, on the portal or renal venous systems. When the patient has adjusted himself to the increased abdominal pressure, the newly created incisional hernia can be easily repaired.

SUMMARY

1. An operation for repair of gigantic hernia has been described.

2. It involves creation of an incisional hernia to handle the immediate increase in intra-abdominal tension. When the patient has become adjusted to this, the newly created incisional hernia is repaired.

TRANSPLEURAL AND EXTRAPERITONEAL APPROACH FOR EXTENSIVE SYMPATHECTOMY AND SPLANCHNICECTOMY

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VARIOUS surgical approaches have been employed for the resection of the splanchnic nerves and the sympathetic chain. Following the initial efforts to accomplish such denervation through anterior root section (1), operations were proposed for division of the splanchnic nerves and extirpation of the first and second lumbar sympathetic ganglia through a subcostal muscle-cutting extraperitoneal subdiaphragmatic approach (2), and for removal of the splanchnic nerves and the lower three thoracic sympathetic ganglia by means of an extrapleural exposure through the bed of the excised eleventh rib (8). Subsequently, convinced that better results could be obtained with a combined supradiaphragmatic and subdiaphragmatic resection, Smithwick (11) introduced such a procedure. In this operation the splanchnic nerves are excised along with the sympathetic chain including the ninth thoracic ganglion at its upper and the first or second lumbar ganglion at its lower limit; exposure is obtained extrapleurally and extraperitoneally by resecting part of the twelfth or eleventh and twelfth ribs and incising the diaphragm from above. Grimson's (4) technique for total sympathectomy is done in three stages. Each supradiaphragmatic operation is carried out transpleurally after removing portions of the third and tenth ribs and in a final transperitoneal operation through a midline incision the lumbar portion of the procedure is completed. With the passage of time, Grimson (5) has tended to omit the transperitoneal part of the procedure and has attempted to remove the first lumbar ganglion from within the thorax. Several have proposed operations (extrapleural) more extensive than Smithwick's and less extensive than Grimson's original procedure (3, 6, 9).

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My initial experiences with transpleural resection of the splanchnic nerves date back to the early part of 1941 before the publication of Grimson's transthoracic operation (4). Desiring to test the effect of vagal denervation in gastric crisis of tabes characterized by prolonged and uncontrollable bouts of vomiting and not realizing at that time that a complete vagal section below the diaphragm could be accomplished with relative certainty, I resolved to do these procedures transpleurally. Being concerned over the possible occurrence of annoying gastric atony following vagotomy, I decided to resect the splanchnic nerves as well. The experience with these first 2 patients convinced me of the ease of complete vagal section and of splanchnic and thoracic sympathetic resection through the transpleural approach. A number of years passed, however, before I again used this method either for vagal or splanchnic denervation.

In operating for hypertensive disease during the past several years, I have employed with increasing frequency a transpleural incision for the thoracic portion and an extraperitoneal exposure for the lumbar portion of the procedure. At the same time my experience with various extrapleural operations has convinced me that the transpleural and extraperitoneal approach is, at least in my hands, an easier and more precise operation and one less likely to be followed by distressing complications. I have come to use this method both for total or near total sympathectomy and also for somewhat less extensive denervations. These operations have proved so satisfactory I have felt it worth while to describe them briefly. I shall not be concerned in this presentation either with the value of sympathetic denervation in the treatment of hypertensive disease, nor with the possible advantage or disadvantage of varying the extent of the denervation, but

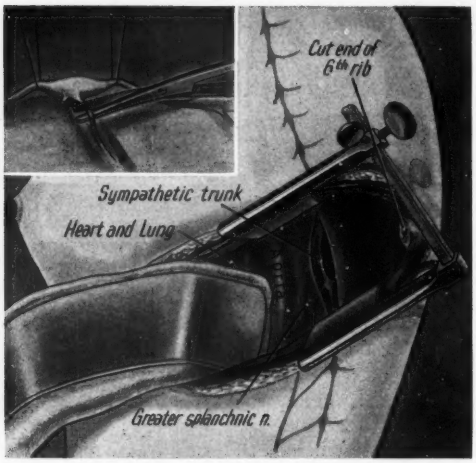

Fig. 1. Drawing illustrating the transpleural resection of the thoracic sympathetic chain and the splanchnic nerves. The insert illustrates the use of traction loops of silk in freeing the ganglia from the underlying intercostal vessels.

only with technical considerations in performing the operation.

TECHNIQUE OF OPERATION

The patient is anesthetized with intratracheally administered ether-oxygen mixture following cyclopropane induction. He is placed upon his left side, with the right arm fixed upon an arm rest and with the trunk stabilized by a broad band of adhesive tape across the hip and attached to both sides of the table. Intravenous infusions of glucose are kept dripping to permit the addition of vasopressors if needed or a transfusion of blood. The skin of the chest and abdomen is prepared widely and draped so as to leave in the operative field the lower two-thirds of the right side of the thorax and the upper half of the right side of the abdomen. For total or near total sympathectomy a long skin incision is made over the course of the sixth rib from about the anterior axillary line in front, back to within a few centimeters of the midline. After clamping and ligating bleeding points and sewing in place skin towels, the latissimus dorsi and serratus magnus muscles are divided and a long segment of the sixth rib is removed subperiosteally back posteriorly to a point beyond the angle. The pleural cavity is entered and the lung is held back mesially with a malleable retractor placed over a moistened pad in such a fashion as to maintain exposure of the paravertebral area and at the same time to permit fairly full rhythmic inflation of the lung. The sympathetic chain and the great splanchnic nerve are ordinarily readily seen through the parietal pleura.

The pleura is incised longitudinally over the mid portion of the sympathetic chain (Fig. 1) and, as the operation is extended, this incision is carried upward and downward over the course of the chain. Using long smooth bayonet or dressing forceps the chain is picked up between the sixth and seventh ganglia, elevated from the underlying vertebra by slipping beneath it the closed blades of a Metzenbaum scissors, and then a loop of silk is placed about the chain with a small curved aneurysm needle. The same process is now repeated between the fifth and sixth ganglia. By gentle traction on the two loops of silk anteriorly and toward the midline the chain is elevated off the vertebra. The closed blades of the scissors are carefully passed underneath the ganglion so as to lift it off the intercostal vessels which lie posteriorly and to develop and put on a slight stretch the rami communicantes. These are now severed. The same process is continued until all the thoracic ganglia are thus freed. When one reaches a point as high as the third ganglion it is sometimes easier to omit the use of the silk traction loops and to free the ganglia and rami by lifting the chain below the ganglion away from the bony structure and with the closed tips of the scissors to tease the ganglion and rami free. The same is true when one is freeing the eleventh and twelfth ganglia. Occasionally a vein of considerable size may cross anterior to the chain, especially near the level of the second or third ganglion. In this circumstance the chain is divided below the vein and slipped upward beneath the intact vessel, or, on occasions, the vein is divided between silver clips. Once the sympathetic chain has been freed up to the cephalad limit desired—beyond the second, or first dorsal or the stellate ganglion—the chain is divided and the dissection is then carried caudally. When the chain has been freed down to the level of

the eleventh or twelfth ganglion the greater, lesser, and least splanchnic nerves are isolated, grasped with a long Kelly clamp, and traction is made in a cephalad direction so as to expose the upper portion of the celiac ganglion. In some instances the splanchnics are severed at the point where they join the celiac ganglion; in other instances the celiac ganglion is removed totally or in part. The sympathetic chain is now freed down below the twelfth dorsal to the neighborhood of the first lumbar ganglion and is divided here by traction upon a clamp placed across the chain.

All of this dissection is generally done with excellent exposure. The field is ordinarily well illuminated by a carefully adjusted overhead spotlight. If the apical area is not well illuminated the light can be directed into this region more effectively at times if one tilts the head of the table downward into Trendelenburg position. Or, if one prefers, he may use a Cameron light or a lighted retractor. The lower portion of the dissection is facilitated by the insertion of a long narrow Deaver retractor underneath the incised parietal pleura. This maneuver lifts the pleura and the diaphragm away from the vertebral structures so that the lower end of the chain and the splanchnic nerves are readily seen. Especial care must be exercised in dissecting free the lower part of the chain since in the region of the eleventh and twelfth ganglia it is often delicate even when it is large in the upper dorsal area. As a rule, little or no bleeding is encountered. If a slight ooze is noted in the bed from which the chain has been removed a piece of gelfoam or other hemostatic agent is held firmly against the spot for a few moments. Should a distinct bleeder be encountered it is clipped with a silver clip. At the conclusion of the procedure the edges of the parietal pleura are approximated with interrupted silk sutures, the pleural cavity irrigated with normal saline solution, the lungs expanded fully, and a little penicillin solution introduced. Interrupted silk sutures are placed through the cut edges of periosteum and pleura, the ribs brought together with a rib approximator, the sutures tied and cut, and the closure completed in layers with interrupted sutures of silk. A catheter left in place during closure is now aspirated and withdrawn.

The attachment of the adhesive tape to the front of the table is now loosened so that the patient's left hip can be slid forward and the right hip rocked backward in such a way as to posture the abdomen in an anterolateral instead of a true lateral position. An oblique incision is made extending downward from the tip of the twelfth rib over the course of the external oblique fibers, the three muscle layers —external oblique, internal oblique, and transversalis abdominis—are split in the direction of their fibers and extraperitoneal dissection is carried down to the vertebral bodies where the sympathetic chain is identified. A loop of silk is slipped around it with an aneurysm needle to permit traction upon it, the rami to the ganglion are severed and the chain is excised. The upper limit of the dissection is carried cephalad between the diaphragmatic crura and the first ganglion is freed. Once this is accomplished the previously divided upper end of the chain is readily brought into view (Fig. 2). In some cases the lower limit of the resection has included the fourth ganglion, in others the third. Ordinarily no bleeding is encountered. If a vessel is severed it is clipped with a silver clip. In the rare case in which a vein crosses anterior to the chain it is preferable to slip the divided chain underneath the vein rather than to divide the vessel. The wound is closed in layers with interrupted silk sutures.

In a period of from 7 to 15 days the second procedure is carried out on the left side. Operation upon the right side is performed first by preference since the patient is more likely to have a serious fall in blood pressure during the second procedure and since the operation can generally be accomplished a little more easily and rapidly on the left than on the right side. Two factors are largely responsible. First, the thoracic portion of the procedure is facilitated by the fact that the parietal pleura in the paravertebral area is less firmly fixed to the underlying bony structures due to its relatively loose reflection over the aorta and esophagus. Consequently the divided pleural edges are more readily dissected off the chain and the great splanchnic nerve and are also

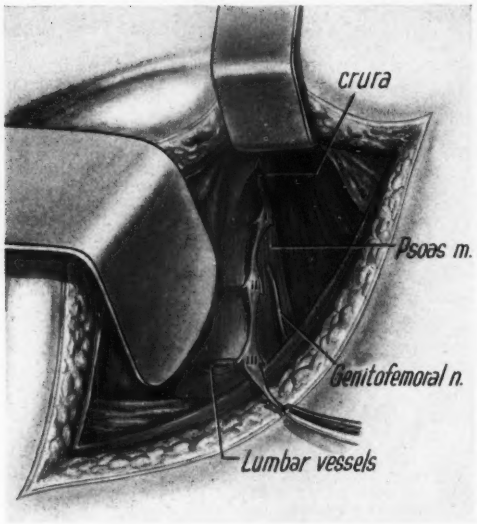

Fig. 2. Drawing illustrating extraperitoneal resection of the lumbar sympathetic ganglionated chain.

approximated with more ease at the conclusion of the procedure. Secondly, the lumbar portion of the operation is somewhat easier since on the right side the vena cava overlies the chain and must be lifted off it and kept gently retracted out of the way, while, on the left side, in contrast, the chain usually lies lateral to the edge of the aorta. Each stage of the operation generally requires an operating time of approximately 2 hours; occasionally it can be completed a little more rapidly; occasionally it requires more time.

For a somewhat less complete thoracolumbar sympathectomy the patient is anesthetized and postured upon the operating table in the manner described for total sympathectomy. The thoracic incision, however, is placed over the eighth rib instead of the sixth. The pleural cavity is entered through the bed of the resected eighth rib. The sympathetic chain and the splanchnic nerves are dissected free and are excised; the resection includes at its upper end either the fifth or sixth dorsal ganglion. The lumbar portion of the operation is then carried out. This more limited operation proceeds with a bit more facility than the total sympathectomy, in part because the thoracic incision is made and closed more easily, in part because of the elimination of the upper thoracic resection with the necessary change in the position of the pads, retractor, and overhead light, and in part because resection of the lower portion of the thoracic chain and the splanchnic nerves is a little simpler through this exposure. Each stage of this type operation requires from three-quarters of an hour to an hour and a quarter for completion.

DISCUSSION

The technique for total or near total sympathectomy has been employed bilaterally in 21 patients and one side in 3 additional patients. The technique for extensive but not total thoracolumbar sympathectomy has been performed upon both sides in 4 patients and upon one side in 2 additional cases. Thus, the procedures described have been carried out 55 times in 30 hypertensive patients. One patient died following the first stage of a thoracolumbar sympathectomy in which the chain was removed from the fifth thoracic ganglion down through the fourth lumbar. She was very ill with malignant hypertension, had almost constant excruciating headaches and vomiting and was obviously a desperate operative risk; the decision to operate was made with reluctance because of the persistent pleading of the patient and her family in spite of the poor prognosis given. She died after a convulsive episode and at autopsy there was evidence of marked cerebral edema. The thoracic portion of the operation has been used bilaterally in 3 and unilaterally in 3 additional patients for indications other than hypertensive disease. The 30 patients with hypertensive disease treated by the technique outlined constituted, I believe, an average group of patients subjected to surgical therapy. Their mean age was 42 years; 3 were in their twenties, 8 in their thirties, 11 in their forties, and 8 in their fifties.

Postoperative complications attributable to the operative procedure included lobar atelectasis in a few cases. This difficulty was easily handled by tracheal aspiration or simpler measures and only in 1 instance proved troublesome or prolonged hospitalization. Occasionally there was an accumulation of serous,

hemorrhagic, or serohemorrhagic fluid which required aspiration. In no patient did any serious difficulty follow; in all, the fluid was resorbed and none developed empyema or required decortication. There were no wound infections. There was 1 hematoma in an abdominal incision. Some patients had little or no pain; some complained of a pleuritic type of thoracic pain. In general, however, it was my opinion and that of the resident staff that significant chest pain was encountered less often and was less severe than in those patients whom we have treated by extrapleural operations. Furthermore, other thoracic complications, including atelectasis, pneumothorax, hemothorax, and pleural effusion, were more common in those in whom the extrapleural approach was used. The problem of thoracic pain has been minimized to a very real degree by the use of intravenously administered calcium.[1] Though a very rare patient has not had any considerable relief with this medication, most of them have noted immediate and marked alleviation of pain. Many have required only 1 injection and rarely have more than 2 been required. Since the use of this medication, no patient has been discharged from the hospital with any except the most trivial chest pain.

For some particular individual reason 4 patients were sent home between the first and second operations; they were discharged from 9 to 12 days postoperatively. In the others the interval between the 2 stages ranged from 7 to 17 and averaged 11.5 days. The patients were discharged in from 8 to 35 days after the second operation; the average was 16.5. Most of the delay was occasioned by a period of waiting for an abdominal belt when such support was required because of postural hypotension. Those delays have been largely avoided since I have been using a simple belt which can be made to measure within a few hours in the hospital workshop (10).

Perhaps other surgeons will find other approaches for extensive or total thoracolumbar sympathectomy preferable. My experiences have, however, made me strongly favor the approach described because of the adequacy with which the nerves are exposed, the direct ease with which any vessels which might prove troublesome can be dealt with, the exactness with which the resection can be carried to the desired extent, and the generally good manner in which the procedure has been tolerated. One may question the use of the additional extraperitoneal approach to the lumbar chain. One can, to be sure, especially if the thoracic incision is reasonably low, retract the diaphragm away from the vertebrae, or deliberately incise it, and resect with reasonable regularity the upper portion of the lumbar sympathetic chain. Personally, however, this attempt has proved rather frustrating because of the inadequacy with which the chain is visualized, and my lack of ability always to remove the desired portion of the chain. Judging from some of the published data on the puzzlingly limited extent of the area of anhidrosis or high cutaneous resistance resulting from thoracolumbar sympathectomy, one is led to believe that others may also have had some difficulty in removing the lumbar sympathetic chain through incisions above the

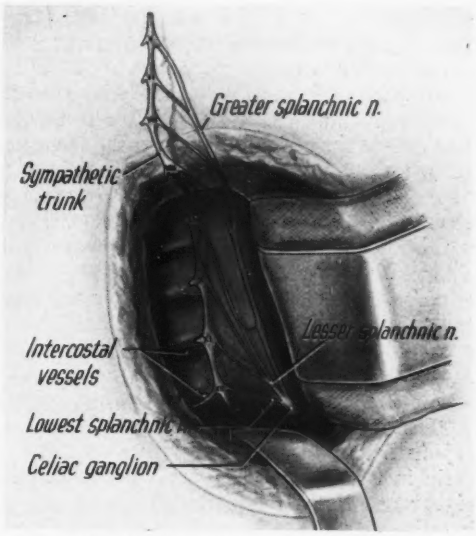

Fig. 3. Drawing illustrating the transpleural resection of the splanchnic nerves and the sympathetic chain from the fifth dorsal ganglion downward.

[1]Ten cubic centimeters of 20 per cent neocalglucon are given slowly, in increments of 2 cubic centimeters intravenously through a small needle. The value of this medication was called to my attention by J. E. Tether who has had a large experience with the use of intravenous calcium in various painful states.

diaphragm. The lumbar extraperitoneal approach adds only from 10 to 20 minutes to the operation, exposes the patient to little or no additional risk, and leaves him with a small muscle-splitting incision which heals readily and causes little if any discomfort. The procedure outlined has one apparent disadvantage, namely, the failure to expose the adrenal glands. Actually with the improved methods of detecting adrenal tumors before operation, I have not felt it necessary to explore the adrenals routinely. For that matter one can frequently palpate reasonably well the upper pole of the kidney and the adrenal area through the abdominal incision. In the occasional instance in which the preoperative studies suggest the advisability of adrenal exploration a slightly lower than usual thoracic incision is used (along with a second higher one if total sympathetic denervation is desired) and the adrenal is explored through the incised diaphragm.

Smithwick has performed total thoracic sympathectomy transpleurally by resecting a long segment of the sixth rib, a small posterior portion of the fifth and a short anterior segment of the seventh rib. He has not felt inclined to perform total thoracic and lumbar sympathectomy in as few as two stages, fearing that the mortality, morbidity, and period of disability would be too great (12). Massell, Ettinger, and Voskamp have recently described a transthoracic approach through the ninth interspace, the lumbar portion being performed from above through the diaphragm. In comparing the convalescence of such patients with another group treated by the extrapleural approach after resection of the ninth or tenth rib, they found that complications were far less frequent in the former group. They laid great stress upon the intercostal incision in the one group and the rib resection in the other. If my own experience is valid, I would tend to feel that the important difference in their two groups may not have been the use of rib resection or intercostal incision but rather the use of a transthoracic approach in one group and an attempted extrapleural procedure in the other. After various thoracic procedures I have not found that patients were more comfortable or had fewer complications when thoracotomies were done without rib resection than when they were done with rib resection. Indeed, except for anterior incisions and for lateral incisions in children, I have generally preferred to do a rib resection because of the greater ease with which a nice closure can ordinarily be accomplished.

SUMMARY

Techniques are described for the performance in two stages of total, or less complete but extensive, sympathectomy and splanchnicectomy by use of the transthoracic and extraperitoneal approaches. These operations seem to be well tolerated and to be attended by a reasonably low mortality and morbidity.

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INFRARED PHOTOGRAPHIC STUDIES OF THE SUPERFICIAL THORACIC VEINS IN THE FEMALE

Anatomical Considerations

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ONE of the major efforts in cancer research has been directed toward early diagnosis. This is as it should be, for regardless of advancements in other phases of investigation the need for selective early diagnosis will always be of paramount importance.

In a previous publication Massopust (10) presented an infrared photographic study of the superficial veins of the thorax in relation to breast tumors. This preliminary report included 100 cases. It was shown that in some cases of breast tumors the appearance and pattern of the superficial veins of the thorax were altered. It was suggested that this method might serve as an additional adjunct in the detection and classifications of tumors of the breast. Studies have continued along these lines and in the near future a complete photographic analysis correlated with clinical findings based upon more than 1,050 cases will be submitted for consideration. These 1,050 cases were referred to us by practicing physicians and surgeons and by the Cancer Detection Center of the Medical Society of Milwaukee County. Preparatory to this report, however, it was considered desirable to direct the attention of the anatomist and surgeon to the confusing anastomoses and extreme variation of the superficial veins of the thorax.

It is not an overstatement to say that we have very little information concerning the architecture and significance of the superficial veins of the thorax.

Many surgeons and anatomists have posed the question: Are there clearly discernible venous patterns in the thorax? If there are, will these patterns permit classification?

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That definite superficial venous patterns exist is indicated by inspection of some living patients, vaguely suggested by photography with ordinary light and incompletely proved by superficial venous dissection. The infrared phlebogram, however, affords a graphic means for study of these patterns in the living.

Massopust in his investigation of applied infrared photography (10) has explained the technique of infrared phlebography. Therefore the principles upon which this study are founded have been presented.

A number of investigators in this country and abroad, have been working independently upon diverse problems related to the application of infrared photography to genetics, pregnancy, neoplasia, and venous dyscrasias of the trunk and extremities. Results have not always been uniform nor conclusive, and have elicited the usual speculation concerning the basic factors involved in these infrared studies, namely the physiochemical response of the vein and its contained fluids to infrared radiation, the structure of vein walls and the role of the overlying tissues. References consulted are listed in the bibliography of this report. However, one quotation seems pertinent to this study. Gorman and Hirsheimer (1939) in reporting upon their infrared studies of superficial veins, discussed the same apparently insoluble speculations which have stimulated the present inquiry. They observed, "There is a marked dissimilarity of venous pattern among all the subjects photographed. The individual subjects among the illustrations show a wide variety of pattern." Their concluding observation was: "The pattern of the superficial venous system should show almost as much variation as is found in the ridges of the finger-tips." If this is true, it is quite likely that the superficial venous patterns of the thorax might be classified by a method

similar to that employed in the classification of fingerprints.

The major emphases of this study have been on the following: (1) an historical and somewhat discouraging survey of atlases, monographs, regional and systematic books on anatomy; (2) morphological dissection studies of both sexes on the routinely embalmed medical school cadaver; (3) study of the living female by: direct observation in the clinic and in the photographic laboratory with ordinary light photography and infrared phlebography; (4) observations by associated surgeons of the faculty and the community in general as they followed their cases; (5) information from dissection of pathological breasts, either at autopsy or in the fresh state by pathologists subsequent to radical mastectomy.

In any new method applied especially as an adjunct to classification or diagnosis the method must be standardized so that there may be a common denominator between the original investigators, confirmatory workers, and the physician who ultimately may use it. Therefore in the following section the technique of reading the infrared phlebogram is presented. An attempt is also being made herein to develop an anatomical basis for careful analysis of the thoracic phlebogram while in a future report the differential classifications of mammary neoplasms will be considered.

REVIEW OF PHLEBOGRAPHIC TECHNIQUE

This has been completely described by Massopust in the past and modified by others (2, 3). Therefore, only a summary of the technique is included in this report for purpose of completeness.

The photograph is made on Eastman infrared sensitive film or plates. A Wratten No. 87 filter is placed over the lens when making the exposure. The back of the camera is tilted slightly upward to bring the plane of the film parallel with the plane formed by the protruding breasts. This is particularly necessary if the breasts are large.

The most convenient and efficient source of illumination for use with the infrared sensitive emulsions is the incandescent tungsten filament lamp. The patient is illuminated from each side by a vertical bank of five 100 watt lamps directed toward the chest at an angle of about 45 degrees, 36 inches away from the patient, and two 500 watt lamps directed toward the chest at an angle of about 45 degrees, 36 inches away from the patient. It is important to strive for flat illumination for very slight differences of light intensity are recorded with extreme contrast on the infrared sensitive emulsion. Movement is controlled by asking the patient to stop breathing. The exposure time is ½ second. Infrared sensitive emulsions are loaded and processed in total darkness.

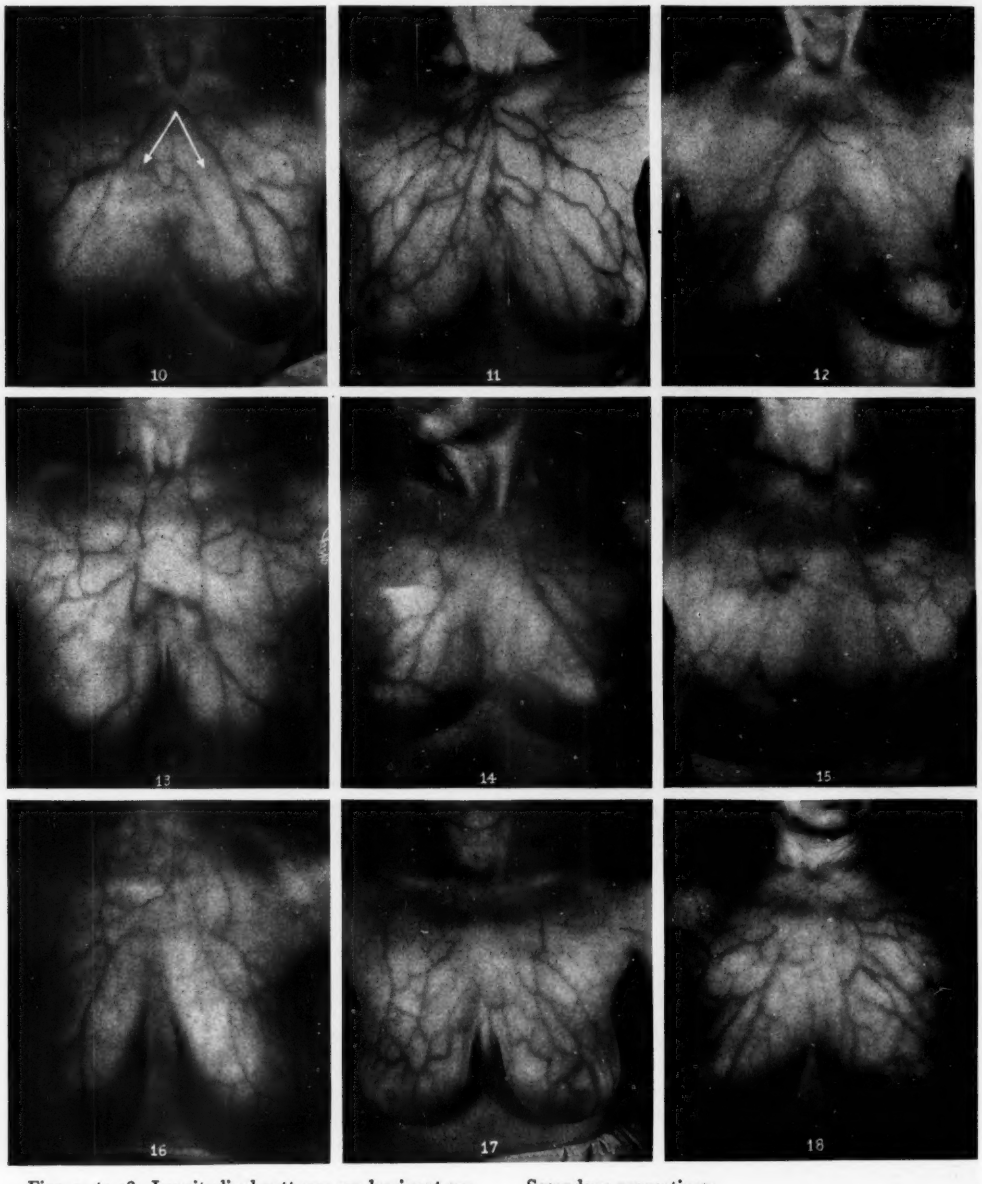
ANATOMICAL BASIS FOR PHLEBOGRAPHIC PATTERNS

The superficial venous network of the thorax has generally not aroused the interest of anatomists. An outstanding systematic treatise (13) dismisses the matter with the following: "The superficial veins of the thorax . . . form a plexus over the entire chest of which the portion over the mammary gland is called the mammillary venous plexus. The lateral thoracic vein drains the mammary plexus, the costoaxillary, the thoracoepigastric veins and terminates in the axillary vein. The veins nearer the median line are drained by the internal mammary vein and its anterior intercostal and superior epigastric tributaries. The veins over the entire thorax are in free communication with the superficial veins of the abdominal wall that drain into the great saphenous and femoral veins and into the deeper veins of the abdomen." This differs very little from the similar section of the same treatise written 35 years before (11).

Dissection of the superficial veins is difficult because of the small size of the vessels especially when they are collapsed. They are in the way of the dissector's advance upon other more important structures. They are not readily apparent in the living. In cases of obstruction in the great abdominal venous systems where they become more dominant as collaterals by virtue of their anastomoses, significant morphologic studies have not been made. In the female the mammary arterial supply has been of importance to the surgeon and thereby has received considerable attention. But even in these vascular studies of the

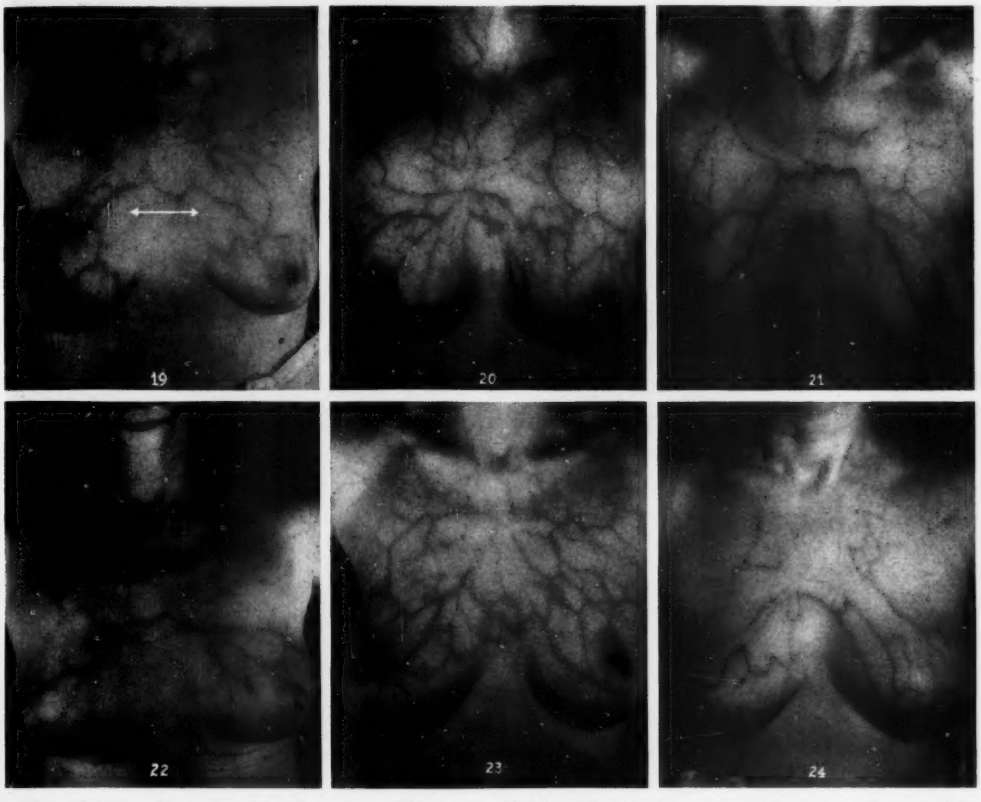
Figs. 1 to 9. Transverse patterns, predominant convergence of the pattern is at the midline of the thorax. Note the secondary anastomotic connections:

Figures 1, 2, 8, and 9, transverse clavicular; Figures 3, 4, 6, and 7, transverse lateral; Figure 5, transverse superior.



Figs. 10 to 18. Longitudinal patterns, predominant convergence is at the suprasternal notch or to the clavicular regions.

Secondary connections:
Figures 11, 13, 14, 15, 17, and 18, longitudinal transverse; Figure 16, transverse clavicular.

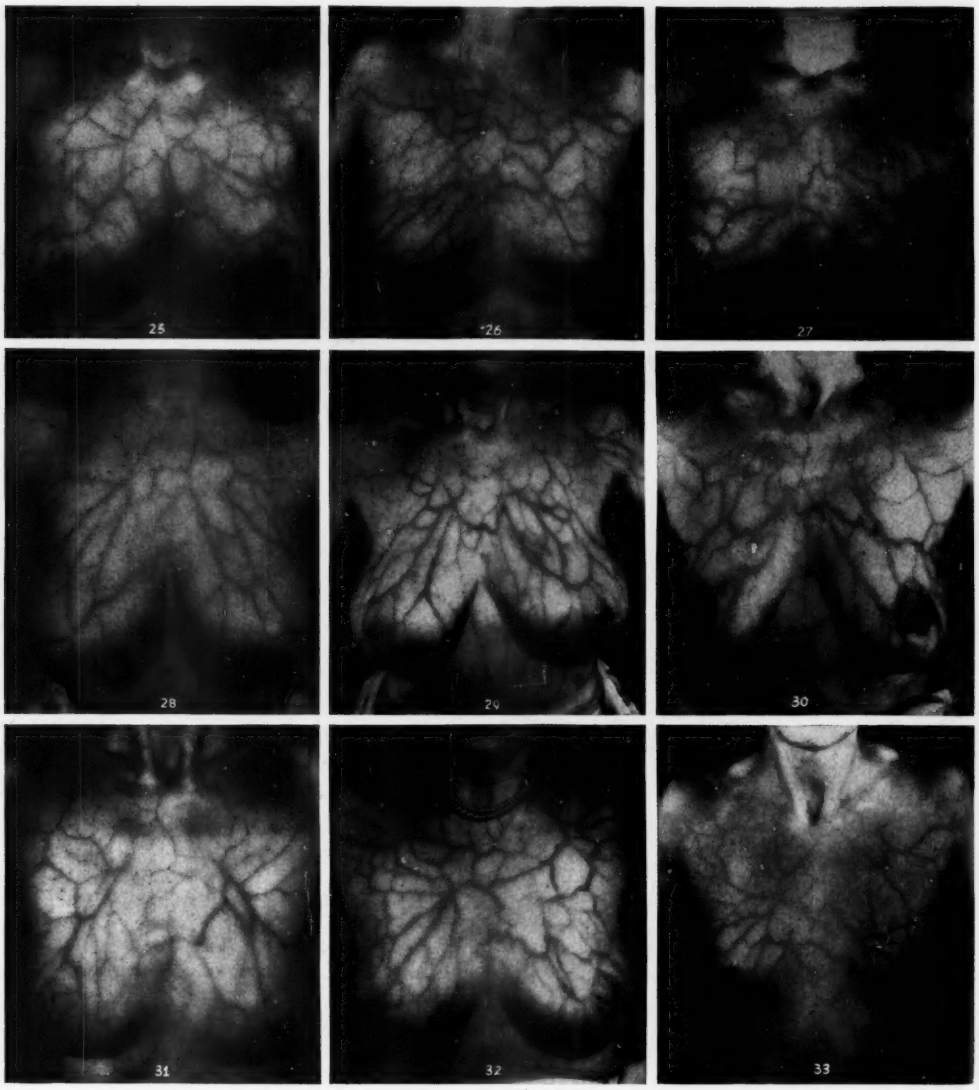


Figs. 19 to 24. Transverse lateral patterns. There are direct connections crossing the midline of the thorax. Note the similarity in Figures 19 and 22, 20 and 23, and in Figures 21 and 24.

breast the venous system has been dismissed as being of little importance. Hence the literature is scant in references, anatomical atlases are vague except for descriptions of the larger anastomotic vessels, and the texts discouraging in their brevity.

The superficial veins do form a plexus over the entire thorax. This is especially evident in the male and in the preadolescent female (Fig. 45). With the development of the mammary glands the portion of the thoracic plexus overlying the breast becomes adapted for drainage of these glands. In this process the veins of the mammary area become conspicuous and form the mammary plexus. Their connections and anastomoses, however, are unchanged for the mammary plexus is not an entity in the female but a specialized portion of the entire superficial thoracic plexus. Another such specialized area is the venous circle of Haller serving the areola and nipple. (Figs. 49, 50, 51). In some females in our series there is persistence of the general male or preadolescent pattern in which the mammary plexus is not prominent or dominant but seems to form a regular diffuse overall pattern.

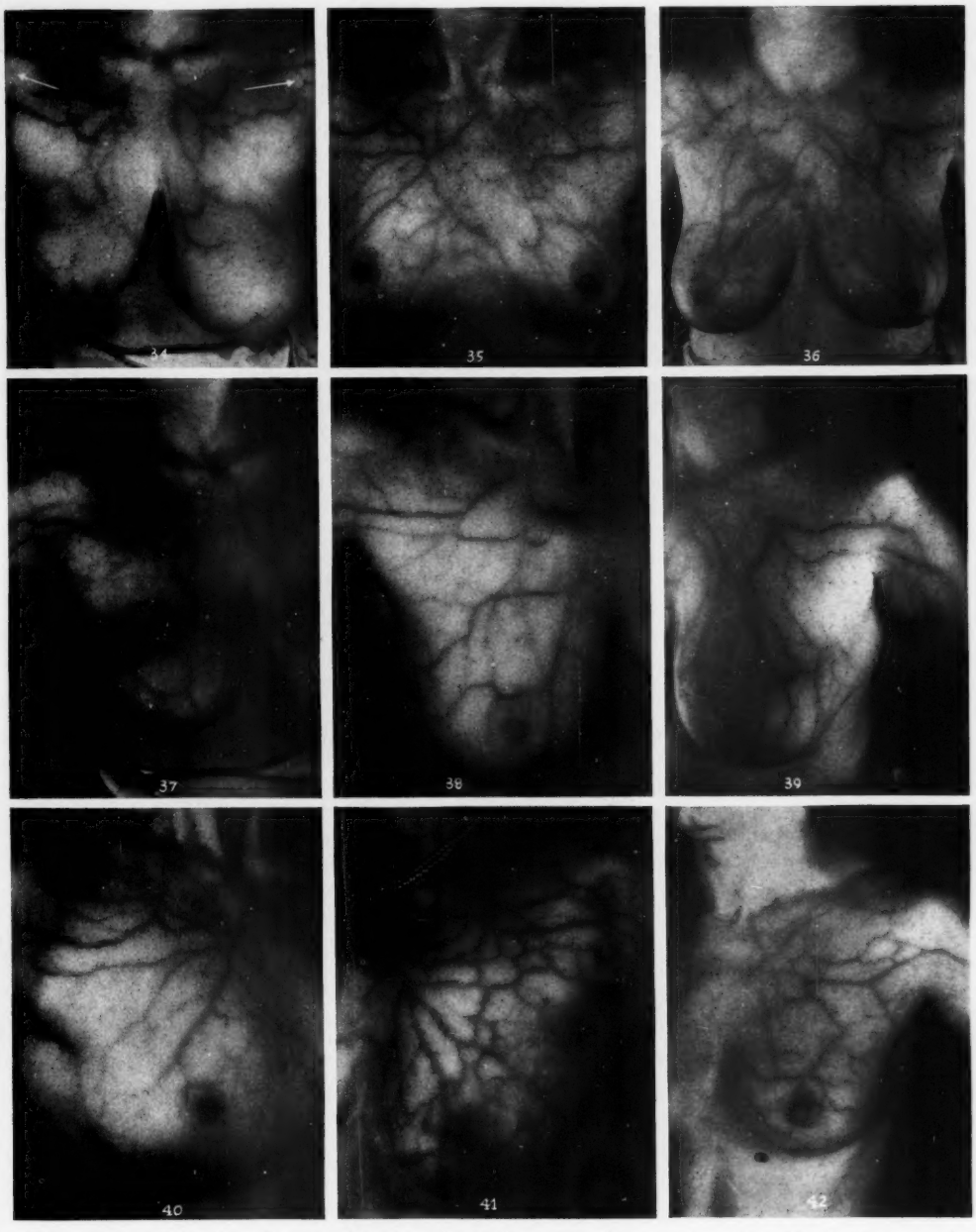
Since the superficial veins are found between the layers of the superficial fascia immediately beneath the skin they are well within the range of penetration of the infrared rays and are easily discernible by this technique. These veins drain the superficial thorax by anastomosing with the superficial veins of adjacent ventral or lateral area; by becoming



Figs. 25 to 33. Transverse and longitudinal patterns, in which the superficial veins form a diffuse network over the entire thorax.

tributaries to other superficial thoracic veins which connect with deep vessels; or by their own perforating branches which become tributaries to deep veins. The connections of the superficial veins of the thorax as presented in current anatomical sources may be summarized:

1. Superficial venous drainage to the midline of the thorax. This is accomplished by: (a) penetrating branches joining the anterior intercostal veins which contribute to the internal mammary vein; (b) perforating tributaries directly to the internal mammary veins;



Figs. 34 to 42. Veins from the upper lateral portion of the venous plexus anastomosing with subcutaneous veins of the arm.

(c) in the lower thoracic area by superior epigastric tributaries to the internal mammary veins.

2. Superficial venous drainage to the front of the neck. Veins of the plexus over the upper anterior portion of the thorax may drain: (a) by traversing the sternoclavicular joint to penetrate the suprasternal notch into the suprasternal space of Burns where they can join portions of the jugular venous arch; either the transverse communicating portion of the arch or the lateral continuation of the anterior jugular vein may receive the tributaries; (b) lateral to the midline subcutaneous anastomoses can ascend over the clavicle to drain into the plexus of superficial veins of the neck on the outer surface of the platysma muscle; in this case ultimate drainage would be to the varied arrangement of the jugular veins.

3. Lateral drainage. The axillary vein eventually collects the blood from the lateral aspect of the superficial thoracic plexus. The paths concerned are: (a) from the mammary plexus directly into the lateral thoracic vein; (b) via the costoaxillary veins which are tributaries to the lateral thoracic vein; (c) small veins from the plexus may communicate with the thoracoepigastric vein which opens into the lateral thoracic vein; (d) veins from the upper lateral portion of the plexus may freely anastomose with subcutaneous veins of the upper portion of the arm with the drainage thereby becoming that of the upper arm.

4. Atypical drainage. The many variations mentioned in the atlases, monographs, and texts are constantly encountered. In this study some of the aberrant patterns of Toldt and McMurrich have been found frequently enough to be considered in the range of normal percentages.

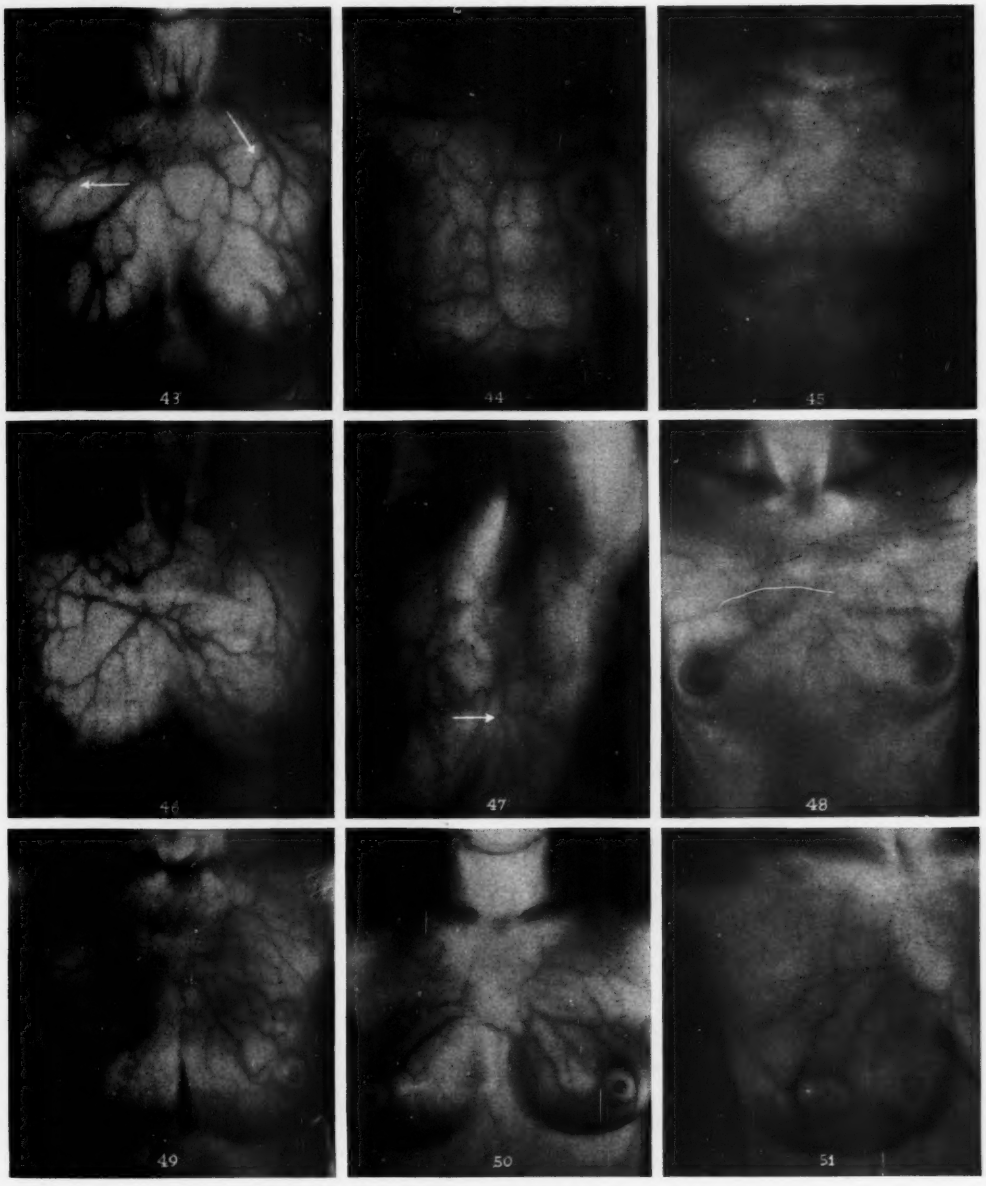
THE THORACIC PHLEBOGRAM

The difficulties encountered in attempting to analyze or classify the thoracic venous pattern have been indicated by Gorman and Hirsheimer. The extreme variation found in individual patterns and the confusing factor of abundant anastomoses seen surgically and in the phlebogram seem to preclude reasonable classification. Prolonged study of this large series of cases however brought forth several common denominators upon which such classifications can be based.

Each thoracic phlebogram must be considered as a whole. Minor points of detail must be disregarded. Only then can general patterns be seen in the network. Massopust originally visualized this pattern of veins as radiating from a central point. Upon this basis he recognized a longitudinal pattern which "radiates in a fan-like pattern downward and laterally into the breast from the point where the anterior jugular vein connects with the arch of the jugular vein, and a transverse pattern which radiates laterally in both directions from the pectoral venous plexus toward the axillary and costo-axillary regions." This conception of radiating patterns is a most useful starting point although it is obvious that it is opposed to the principle of tributary convergence in venous flow. He describes the transverse pattern as radiating laterally in both directions from a central point. However the venous blood contained in the vessels forming the pattern is actually draining via converging tributaries toward this central point, the pectoral venous plexus. Although it might seem wise to follow physioanatomical principles as closely as possible in attempting to classify the variant patterns, such a basis was abandoned as being cumbersome and unsuitable, after many attempts to develop suitable terminology. Therefore, Massopust's original suggestion of visualizing the phlebogram as a pattern has been retained for purposes of classification.

On this basis the superficial venous patterns are classified into two principal groups: (1) the transverse pattern—patterns with predominant convergence to the midline of the thorax (Figs. 1 to 9); and (2) the longitudinal pattern —patterns with predominant convergence toward the front of the neck or toward the clavicles (Figs. 10 to 18).

With the initial predominant direction of the converging pattern established, the phlebogram is then inspected to determine whether there is a dominant site of secondary anastomoses. These secondary anastomoses may be of two types: small vessels which increase in caliber as they course in the predominant directions of convergence as tributaries



Figs. 43 to 51. Figs. 43, 44, 45, and 46, transverse pattern on the right side of the thorax, longitudinal pattern on the left; Figs. 44, 45, 46, and 47, secondary anastomotic connections laterally; Fig. 45, juvenile pattern, age 10 years; Fig. 48, age 19 years; Figs. 49, 50, and 51, show the venous circle of Haller.

CLASSIFICATION OF 1,050 CASES INTO ANATOMICAL PATTERNS

Analysis of the two principle venous patterns	No. of cases	Per cent
Transverse pattern Patterns with predominant convergence at the midline of the thorax.	953	90.80
Longitudinal pattern Patterns with predominant convergence at the suprasternal notch with no dominant site of secondary connections.	97	9.24
Detailed analysis transverse pattern		
Primary transverse	334	32.00
Transverse clavicular	412	39.20
Transverse lateral	119	11.20
Transverse superior	88	8.40
Analysis longitudinal pattern		
Primary longitudinal	26	2.47
Longitudinal transverse	25	2.40
Longitudinal clavicular	38	3.61
Longitudinal lateral	8	0.76

in the general pattern or vessels which increase in caliber away from this point to connect with vessels outside of the thoracic area.

It is realized that in such a diffuse network of veins as is found in the superficial thoracic plexus, there are delicate venous anastomoses at all borders of the area. These are disregarded in attempting classification. Only the well defined dominant site of secondary connections can be utilized in breaking down the variations into subgroups.

Therefore in arriving at the following classification of the varying anatomical patterns of the superficial thoracic veins in the female, the phlebograms were analyzed in accordance with two factors: (a) predominant directions of convergence of the venous pattern on each side (either transverse or longitudinal); (b) presence or absence of a dominant site of secondary anastomotic connections (subgroups as outlined in the following).

In this series of 1,050 cases only 6 were found which could not be classified on this basis. In these the veins did not photograph.

CLASSIFICATION OF ANATOMICAL PATTERNS

I. Transverse pattern—patterns with predominant convergence at the midline of the thorax.
   A. Primary transverse—predominant convergence to the midline of the thorax with no dominant site of secondary connections.
   B. Transverse clavicular—predominant convergence at the midline of the thorax with secondary connections at the supraclavicular area.
   C. Transverse lateral—predominant convergence to the midline of the thorax with secondary connections laterally.
   D. Transverse superior—predominant convergence to the midline of thorax with secondary connections at the suprasternal notch.

II. Longitudinal pattern—patterns with predominant convergence at the suprasternal notch and the clavicular region.
   A. Primary longitudinal—predominant convergence at the suprasternal notch with no dominant site of secondary connections.
   B. Longitudinal transverse—predominant convergence at the suprasternal notch with secondary connections at the midline of the thorax.
   C. Longitudinal clavicular—predominant convergence at the suprasternal notch with secondary connections at the supraclavicular area.
   D. Longitudinal lateral—predominant convergence at the suprasternal notch with secondary connections laterally.

DISCUSSION

In a study on the blood supply of the mammary gland, Anson, Wright, and Wolfer (1), it was emphasized that arterial vessels do not reach the gland from the inferior aspect but approach only from the medial and superolateral aspects. The statistical information included with the suggested classification herein indicates that in the usually encountered patterns of venous drainage from the breast and superficial thorax a greater amount of blood is directed either to the midline (primary transverse pattern) or jointly to the midline and the supraclavicular area (transverse clavicular pattern). The less dominant inferior (epigastric) and lateral drainage seems to be mainly concerned with tissues of the chest wall and less with the mammary gland. Study of the various phlebograms illustrated

demonstrates that the important veins draining to the midline also ascend to a higher intercostal level in a mediosuperior course for the main vessels leaving the mass of the breast. Phlebographic evidence then is at once in accord with the conclusions of Anson and coworkers in their arterial study; no important vessels are to be found on the inferior aspect of the mammary gland which is the site of election for incisions and excisions when radical mastectomy is not to be performed although radial incisions to the nipple made in the superior quadrants of the breast would naturally take the arterial patterns into consideration more than the venous. It may be pointed out that phlebographic evidence indicates that less venous bleeding will be encountered if incisions can spare the superomedial quadrant.

SUMMARY

1. The infrared photograph affords a readily available graphic means of studying the superficial venous pattern of the thorax in the living without the introduction of a contrast medium.

2. These venous patterns can be classified.

3. A suggested anatomical classification of the superficial venous pattern of the thorax is presented.

4. This study indicates that there is a wide divergence in the predominant convergence of the superficial veins of the thorax which implies that there is a variation in the principal drainage of the mammary glands.

5. Clinical correlative studies of these venous patterns are continuing, the results of which will be submitted for consideration at a later date.

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THE DIAGNOSIS OF EARLY CARCINOMA OF THE CERVIX

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DURING recent years, malignant disease has received increasing interest from the physician. With the advent of agents which control most forms of infectious disease, many of them formerly fatal, death due to neoplasm has moved near the top among the causes of mortality. Among women dying of cancer, one-third succumb to neoplasms, primary in the uterus. Of these, cancer of the cervix makes up 85 per cent of the total. Here we have a malignant tumor arising in an area available to inspection and palpation, and almost as accessible to biopsy and surface scrapings as the skin itself.

Clinically recognizable cancer of the cervix, as a rule, offers no difficulty in detection. The ulcerative and proliferative forms can readily be recognized by sight and touch, and the diagnosis can be confirmed easily by biopsy from the area involved. The problem in these cases has not been one of recognition, but of detection of the lesion at a stage when it can be adequately treated by radiation or surgery. In spite of strenuous efforts, the proportion of stage I cancer of the cervix in most efficiently conducted gynecological clinics rarely rises above 10 per cent. At Bellevue Hospital, over a considerable period of time, the incidence of such cases is 6 per cent—the vast bulk of cervical carcinomas being placed in stages III and IV. The comparative rarity of stage I cancers was the basis for the former belief of the majority of gynecologists, that this lesion developed rapidly and explosively with early invasion. Norman Miller, having studied the problem, points out other factors. He found that an average of 7 months elapsed before a patient sought treatment, while a further delay of 11 months took place before treatment began. On the other hand, it is commonplace to see advanced cancer of the cervix with a very brief preceding history of symptoms. In short, should we continue to regard stage I cancers as the earliest manifestation of the disease, there seems to be little chance of improving our therapeutic results—whether by radiation or by radical or ultraradical surgery.

However, during the past 20 years, a newer concept of the early stages of this tumor has gradually won acceptance until today it is opposed only by a minority. It is to the effect that cancer of the cervix may exist, in many instances, if not in all, for a period often prolonged, as a lesion confined to the covering epithelium. This preliminary stage of cancer of the cervix is termed variously, carcinoma in situ, intraepithelial cancer, or preinvasive cancer. Only when it develops its terminal invasive stage is its progress likely to become rapid and violent. Granted that this belief is correct, the earliest case which can be recognized clinically must be regarded as one in the final stage of the disease. The fact that radical surgery is deemed necessary for these cases is evidence of the truth of this statement.

To review briefly the history of this concept, it may be said to have its beginnings in the studies of Schottlaender and Kermauner, prior to 1912. Their investigations began with their interest in the peripheral portions of invasive cervical cancer, which they found to be composed often of a layer of neoplastic cells, confined to the surface, and often joining the normal epidermal tissue abruptly and at an oblique angle. During these studies, cases were encountered in which lesions were found to be entirely limited to the surface layers, or with only slight evidence of invasion. Rubin, one of their postgraduate students, published observations on 3 of these cases in 1910 on his return to this country. Another of these young associates was Walter Schiller (16, 17, 18) who became deeply engrossed in the early stages of cervical cancer through the rest of his life. Recognizing the futility of attempt-

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Fig. 1. Case 16. The only instance of significant visible lesion. The abnormal layer of epithelium is thrown into convoluted folds to form a small flat papilloma. The basement membrance is intact. Early invasion was demonstrated elsewhere in the cervix. ×30. (See Fig. 14.)

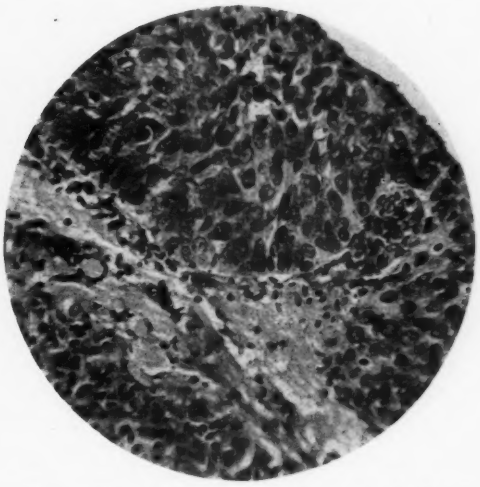

Fig. 2. Case 2. Basement membrance is clearly demonstrated, but the overlying cells show definite neoplastic change and loss of stratification. Variation in nuclear size and shape is evident, and the chromatin is heavily concentrated. ×300.

ing to recognize these lesions by ordinary clinical methods, he developed the Schiller test as a means of differentiating the neoplastic areas from normal tissue. Unfortunately, it proved to be nonspecific. He also used scrapings from the portio vaginalis as a diagnostic aid. In his first paper published in 1927, he pointed out the location, the morphological character, the abrupt junction with normal tissue, and the reaction of the underlying stroma, manifest in early preinvasive cancer of the cervix. He regarded this change as an abrupt metabolic affair, unrelated to irritation, infection, injury or repair, and believed it to be irreversible. Schiller's beliefs were opposed by the majority of gynecologists and pathologists who were convinced that evidence of invasion must be one of the prime requisites in the diagnosis of a malignant tumor. Early converts among clinicians were Smith and Pemberton, of the Free Hospital for Women in Brookline, Massachusetts. As a result, Younge, Hertig, and Armstrong, in 1949, were able to report from this institution 135 examples of this lesion. In 1938 Stevenson and Scipiades reviewed sections prepared from 3,000 cervices and discovered 18 such lesions, (0.6%). Furthermore, when such areas were left untreated or inadequately treated, they were able to show that many of them developed into invasive cancer. In 1943 Knight reported 11 cases discovered in reviewing the pathological material at the Sloane Hospital for Women. Pund and Auerbach (13), in 1946, discovered 47 instances in 1,200 cervices (3.9%), examined by meticulous pathological methods. TeLinde and Galvin, in 1949, reported 66 instances of this lesion discovered clinically by the liberal use of biopsy. Numerous reports of isolated instances and smaller series have appeared in the recent literature.

In addition, about 18 cases (24) have been assembled in which this localized lesion has been observed to develop into an invasive tumor, sometimes after an interval of many years. This transition has been allowed to take place by intention, by refusal of the patient to submit to treatment, by incomplete therapeutic measures, or by error in the interpretation of the original biopsy. One such case, reported by Taylor and Guyer, has been observed at Bellevue. This woman, after a cervical biopsy diagnosed as chronic cervicitis was subjected to supracervical hysterectomy

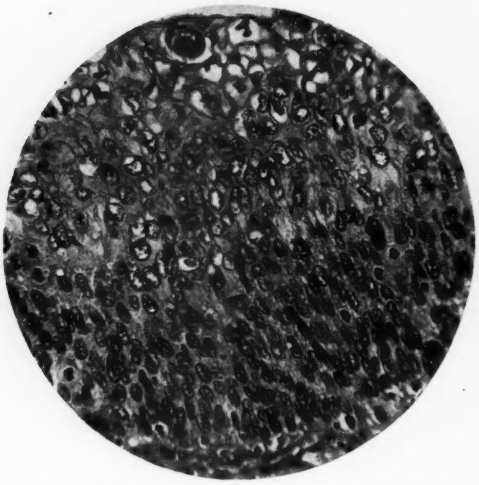

Fig. 3. Case 3. Cell outlines are lost in the lower two-thirds of the squamous epithelium, and there is irregular spacing of the nuclei. Cell polarity is generally preserved, but there is variation in nuclear size and staining. Several multinucleated (Bowen's) cells are present. ×200.

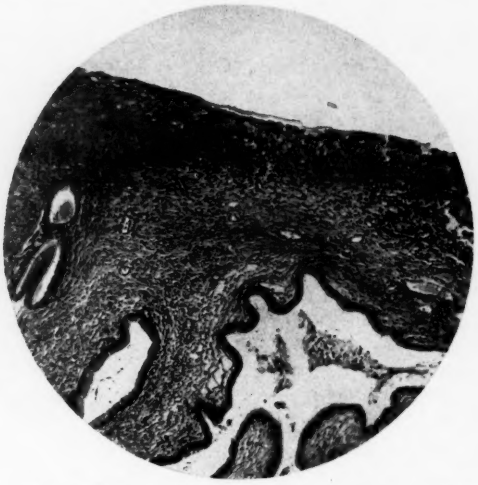

Fig. 5. Case 13. Clearcut junction of normal stratified squamous epithelium and intraepithelial carcinoma, in an oblique line of 45 degrees (Schiller's line). Decreased depth of the neoplastic tissue, as compared to neighboring normal epithelium, is often noted. ×58.

in 1938. In 1945 she was found to have a stage I cancer of the cervical stump. The true nature of the original biopsy was then discovered. One of the most convincing of these cases is that reported by Younge and associates (24). The pathologist refused to make a diagnosis of intraepithelial cancer on a biopsy specimen. Therefore, it was decided to follow the patient without treatment. In 6 months she was found to have developed invasive cancer at the exact site of the original biopsy. The long duration of the preinvasive stage in many of these patients brings up the question as to whether some of these lesions may fail to develop a terminal invasive phase or may be destroyed early in their career by some form of trauma. This possibility is also suggested by the high incidence of intraepithelial carcinoma reported by Pund and Auerbach (13, 3.9%) and by Gusberg (4, 2%). Nevertheless, they present ample evidence of the close relationship of the intraepithelial lesion to invasive cancer. Today we find this relationship accepted wholeheartedly by such eminent authorities in the field of surgical pathology as Stout, Stewart, Foote, Warren, Hertig, Lisa, and many others.

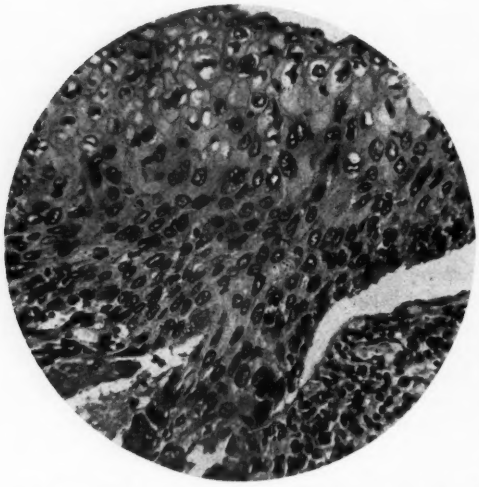

Fig. 4. Case 6. A peg extending downward to seal off the neck of an endocervical gland. Hyperchromatic nuclei are frequent, and there are several abnormal mitotic figures. ×200.

Many of the pathologists who dislike the name, intraepithelial carcinoma, or carcinoma in situ, for this lesion, readily admit that it is a likely or even probable site of future invasive

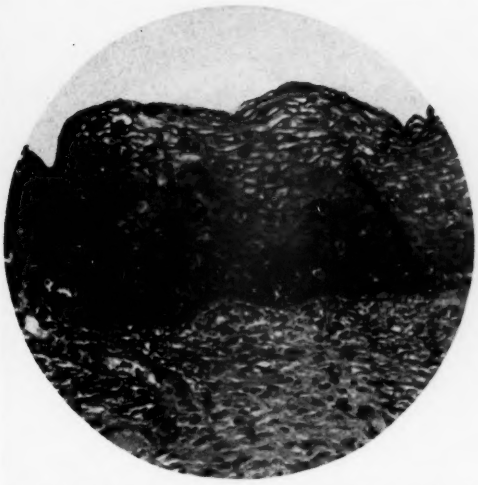

Fig. 6. Case 8. Abrupt transition of normal to neoplastic epithelium at left. There is a zone of abnormal cells in the basal layer, extending upward in small nodes covered by normal cells of the superficial layer. ×87.

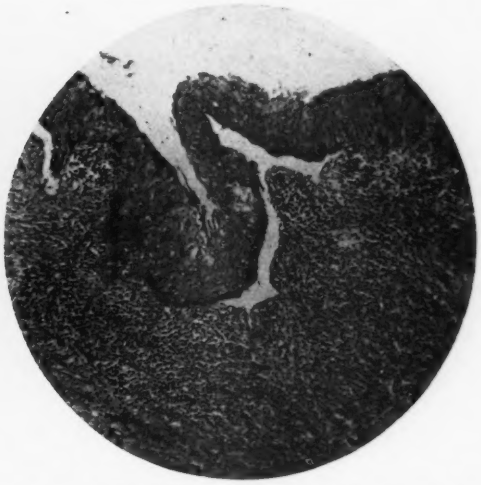

Fig. 7. Stromal infiltration of lymphocytes beneath the lesion. Note the beginning separation of neoplastic epithelium from underlying tissues. This stripping phenomenon is often seen when the lesion is traumatized. ×45.

cancer. A great deal of disagreement therefore stems from dispute over classification and nomenclature, and from a reluctance to consider the lesion as an early form of a highly malignant disease. In this regard, the philosophical concept of Mallory is most useful:

"Such a diagnosis connotes an expression of faith on the part of the pathologist that a given segment of epithelium has undergone the initial stage of an irreversible sequence which can end only in frank invasive cancer. The time at which invasion may begin, however, is quite impossible to foretell and may be years ahead . . ."

Other clinical facts have been gathered from these large series which are of importance. The age of these patients averages about 38 to 40 (23, 24), as compared to the average age of 48 among patients with invasive cancer. The incidence of preinvasive cancer among gynecological patients has been found to approach but not to exceed the incidence of the clinically recognizable invasive cancer (24, 1.6%). While the lesion appears to be irreversible in the nonpregnant woman, instances have been reported of extremely suspicious biopsies removed from the cervices of pregnant women in whom, apparently, reversion to normal took place postpartum (24). Such lesions in pregnant women must, therefore, be viewed with caution. We are just beginning to get rid of our taboo against taking biopsy specimens from the pregnant cervix, and

Fig. 8. Case 13. Example of stripping phenomenon following vaginal hysterectomy. Cancerous epithelium has been stripped away except for a short segment in the center, and plugs in adjacent endocervical glands. ×13.

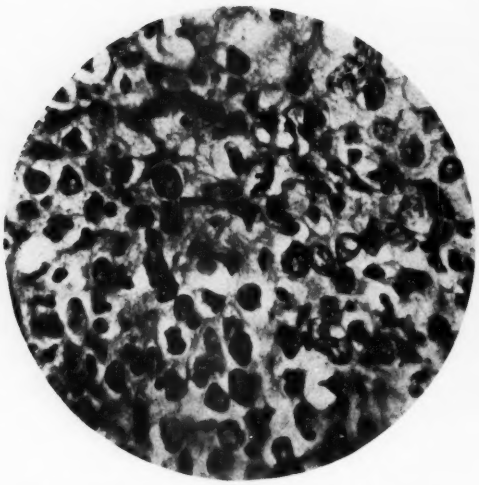

Fig. 9. Case 13. Higher magnification of section showing plug of neoplastic cells filling the gland below the surface in the upper left quadrant of Figure 8. ×256.

Fig. 11. Case 11. Unusually small lesion, occupying the squamocolumnar junction and extending downward into nearby cervical glands. Almost all of the lesion was removed by biopsy. The remaining portio and canal are normal. ×30.

should learn much about its epithelial changes in the coming years.

In the search for intraepithelial lesions, many instances have been discovered of early tumors showing a suggestion of or actual early invasion. These have been included often in reports on intraepithelial lesions, which makes for confusion. The discovery of such lesions, often in symptomless patients with no sign of

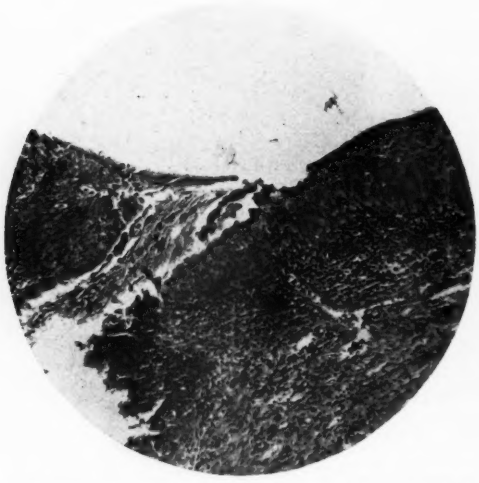

Fig. 10. Case 9. Minute lesion situated at 2 o'clock which escaped detection by biopsy, but which constantly yielded positive cell smears. This lesion was only discovered after examination of the excised uterus. ×87.

Fig. 12. Case 5. Large plug of neoplastic squamous tissue partially filling an endocervical gland. Basement membrance is intact, despite the displacement of endocervical cells. ×45.

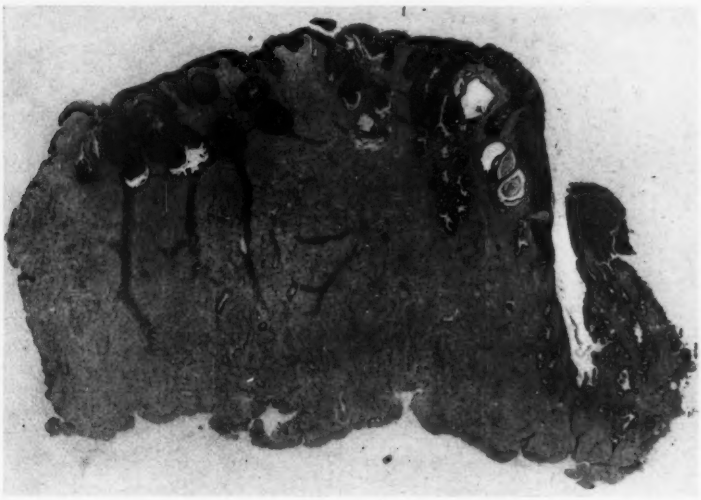

Fig. 13. Case 5. Extensive involvement of portio, endocervical glands and cervical canal nearly to the internal os, by intraepithelial carcinoma. A short strip of normal squamous epithelium adjacent to the lateral fornix is seen at left. This lesion was asymmetrical and occupied only one quadrant of the cervix. ×3.

abnormality detectable by touch or vision, has shaken the gynecologist from his belief that early invasive carcinoma of the cervix can always be recognized by simple bimanual and speculum examination.

The observations which have been outlined have altered our conception of the early stages of carcinoma of the cervix. Instead of being a volcanic lesion from the start, it must be regarded in a considerable proportion of instances, if not in all, as a neoplasm with a fairly prolonged quiescent initial phase, during which it is limited to the surface. Only at the end of this phase does it become invasive, a change which is usually followed by rapid growth and the production of a clinically recognizable lesion. To preserve the value of our present classification of clinical carcinoma into four stages, the addition of another group to contain these cases would seem indicated. This would contain intraepithelial lesions and preclinical invasive tumors or covert cancer, a term suggested by Pund (14). The problem of combatting this type of cancer would be simple, provided an easy and efficient method of detecting its presence was available. At the present time this can only be accomplished by a great deal of hard and meticulous work, 99 per cent of which shows negative results.

Fig. 14. Case 16. Early invasion. The endocervical gland occupying the center and upper left of the field is lined by carcinomatous squamous tissue. A break in the basement membrane has occurred at the gland tip, and malignant cells are pouring through to invade the stroma at this point. ×30.

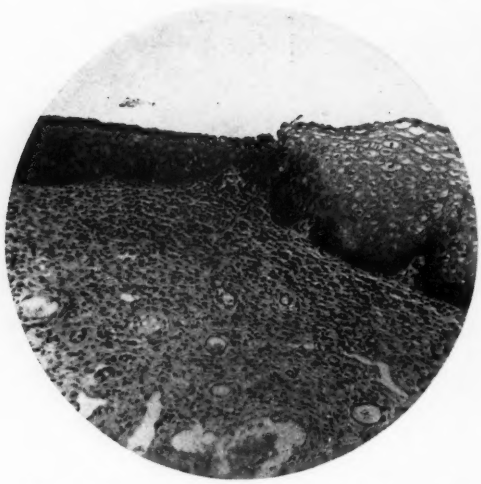

Fig. 15. Case 15. Anterior lip. Junction of normal and neoplastic tissue, with abrupt loss of stratification and malignant changes in the cells of the squamous epithelium at the left. Basement membrance was intact in all sections taken from the anterior lip. ×45. (See Fig. 16.)

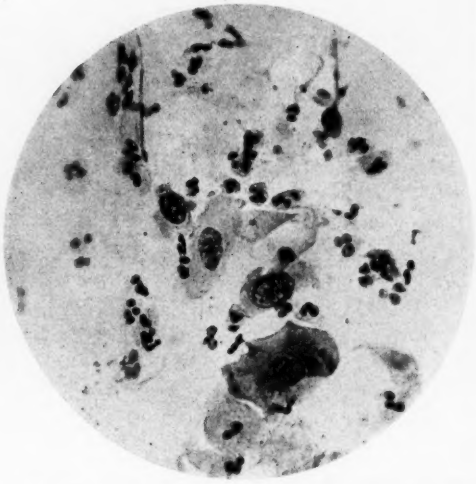

Fig. 17. Case 4. Several malignant cells showing nuclei with sharp borders, irregular masses of chromatin, and variation in size. Fiber-like cells which were similar to that in the lower portion of the field were frequently seen. ×385.

It is obvious, however, that if control is to be obtained over these vicious tumors, they must be discovered in the preclinical stage. The characteristics of these early lesions and the means by which they have been discovered

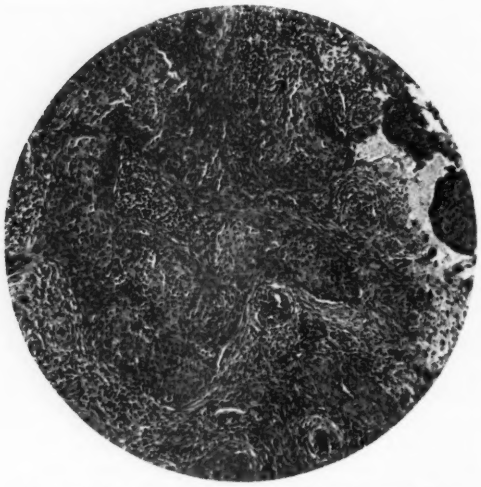

Fig. 16. Case 15. Posterior lip. Although grossly identical to the anterior lip, sections of this area showed an obviously invasive squamous cell carcinoma. ×45.

on the gynecological service at Bellevue Hospital form the basis for our discussion.

During the period between January 1, 1938 and March 31, 1947, only three preclinical tumors were discovered. One of these cases has already been mentioned, an untreated patient, who, 7 years later was found to have a stage I invasive cancer. Of the 2 remaining, 1 was recognized by preoperative biopsy, and 1 was accidentally discovered in a patient subjected to total hysterectomy. Both were in the very early stages of invasion and have been lost to follow-up.

Early in April, 1947, impressed by the reports of Younge and TeLinde, an intensive effort was made to recognize a greater proportion of these lesions. At first this consisted merely in greatly increasing the number of biopsies, particularly on the cervix presenting some deviation from the normal at the squamocolumnar junction. Treatment of such cases was postponed until the laboratory report was obtained. In October of the same year the part time service of a cytological technician was obtained, and the cytological studies of selected cases were commenced. As a result of these two aids to diagnosis, there

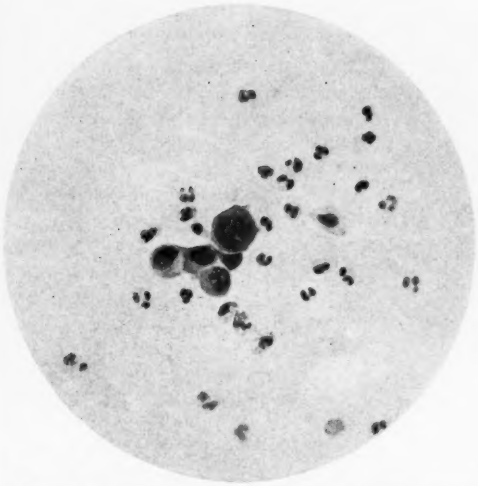

Fig. 18. Case 5. Group of malignant cells with coarse dispersion of chromatin and variable nuclear size. The largest cell contains a nucleus of irregular shape with prominent nucleoli. ×190.

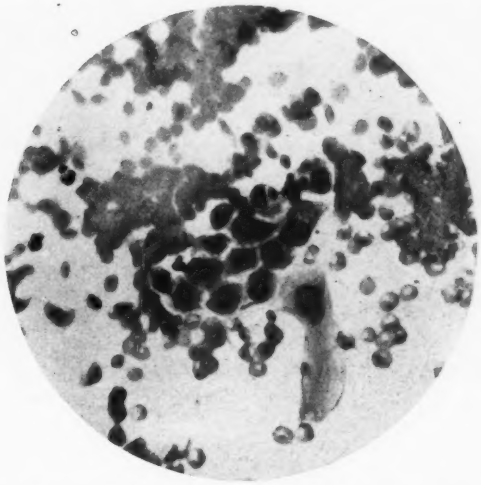

Fig. 19. Case 8. Photomicrograph showing a group of malignant cells with abnormally shaped, hyperchromatic nuclei. Nucleoli are large and prominent in most of the cells. ×255.

have been discovered up to the first of January, 1950, 16 cases, 13 of them intraepithelial in nature, while 3 showed early invasion. In 1 of the latter, this process had barely begun, while in 2 it was well defined. All of them were recognized prior to treatment. Furthermore, although 85 per cent of the hysterectomies have been of the total variety, no example of an unsuspected lesion was found, in spite of careful search. No claim is made that all possible cases have been found. The above record is humbly presented as evidence of progress. Had this lesion been attacked as vigorously between 1938 and 1947, the number of cases discovered would have exceeded 70.[1]

PATHOLOGY

Gross. Only in 1 instance was a significant lesion found on inspection and palpation—a small, flat papillary growth adjacent to the external os. Since 13 of the 16 women were parous, minor lacerations of the cervix were frequent. In 5, a reddish zone, varying in symmetry was described about the external os. These were uniformly interpreted as "erosions." There was a striking absence of cystic cervicitis, or of marked evidence of inflammation among these patients. In most of them, there was no apparent reason for therapy. The consistency of the cervical muscularis

[1]Since January 1, 1950, 4 additional patients have been treated surgically, 2 of them having intraepithelial lesions while 2 had symptomless invasive cancer. Several others have been discovered, and are awaiting operation.

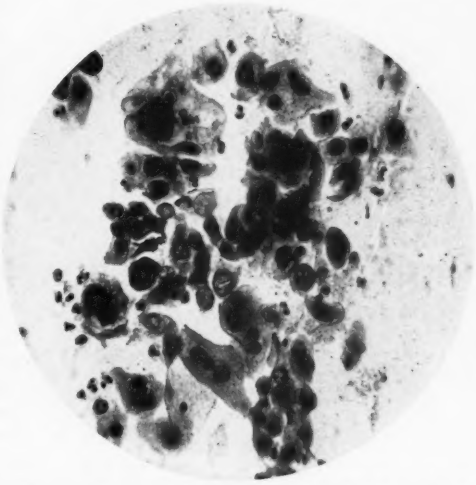

Fig. 20. Case 9. Several multinucleated cells, and cells with huge, bizarre-shaped nuclei are present. Note the variation in nuclear size and staining. ×145.

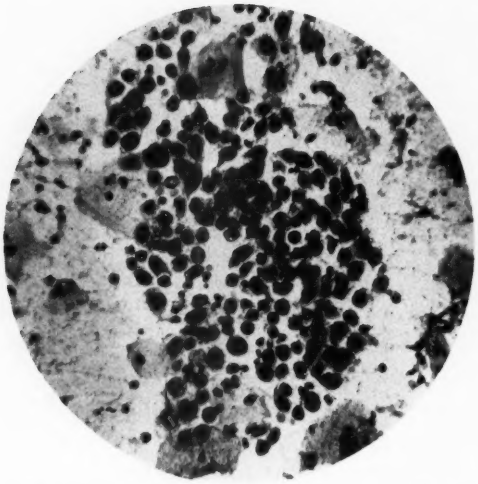

Fig. 21. Case 11. A large group of atypical cells surrounded by normal squamous cells. There is moderate variation in nuclear size, and several large hyperchromatic nuclei with abnormal shapes are present. ×256.

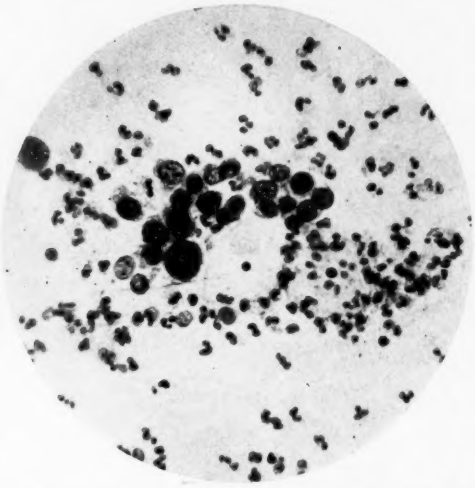

Fig. 23. Case 15. This photomicrograph shows that there is variation in nuclear size and staining. The darker nuclei show masses of clumped chromatin, and unusually large nucleoli. ×256.

was found to be normal in the intraepithelial lesions, but in one of the cases with early invasion, it was described as soft and "fudgy" when incised for purposes of biopsy. In short, agreement was reached with statement of Foote and Stewart, who remarked, after examining 27 intraepithelial cancers of the cervix, that there was no way of detecting the

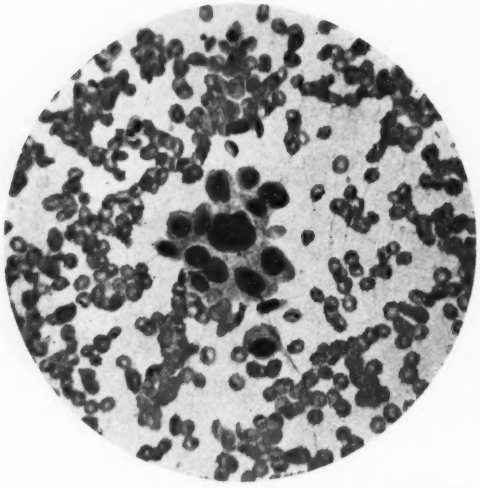

Fig. 22. Case 14. A group of moderately well-differentiated malignant cells. The central cell is abnormal in size and shape and contains several prominent nucleoli. ×256.

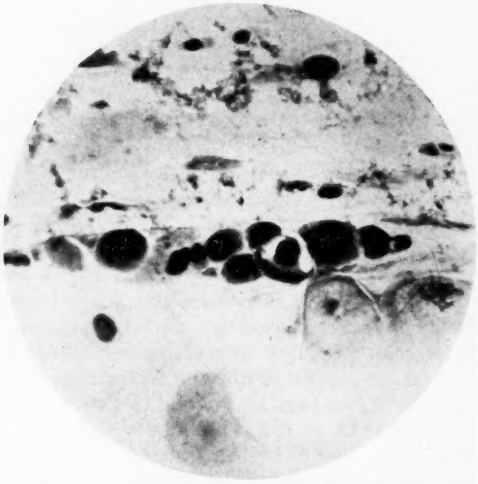

Fig. 24. Case 16. Several obviously malignant squamous cells with very hyperchromatic nuclei. Note the vacuolated cell near the center, with a mass of chromatin flattened against the cell border. ×256.

presence or extent of the lesion by sight or touch.

Microscopic. The cells which make up the covering epithelium of the cervix exhibit the signs generally accepted as characteristic of malignancy. As a rule, this is a flat layer, but in one of our specimens it was thrown up in complex papillary folds to form a small but clinically recognizable papilloma (Fig. 1). This was the only lesion among our specimens which could be detected clinically. There is a complete loss of the orderly layers seen in normal, stratified squamous epithelium (Fig. 2). The nuclei present a total lack of uniformity and often of polarity. Some may be six times the size of neighboring nuclei; they may be round, oval, flattened, slightly curved or twisted (Figs. 3 and 4). Some nuclei will take practically no stain at all, the chromatin standing out prominently like the lattice work over a window. Their nucleoli are unusually large and stain more deeply than those of benign cells. Other nuclei are hyperchromatic and take a deep almost black stain with hematoxylin. All degrees of staining density may be present between these two extremes, as well as intranuclear variations, whereas in normal cells the larger the nuclei the paler the stain. Here is found no relationship between size and depth of stain. Large multinucleated cells may be present. The cytoplasmic borders are not easily defined and the cells themselves are closely packed, giving the impression that a much greater number of nuclei are present per high power field than in normal squamous epithelium. These changes are present right up to the surface, little or no evidence of an attempt to form a compact spinal layer being present. Mitoses, often abnormal, may range from abundant to scanty. Their presence is less important than the architecture of the tissues. Glycogen, normally present in the spinal and some of the superficial transitional cells of normal tissue, can be shown by Best's stain to be absent in these neoplastic cells.

The junction between intraepithelial carcinoma and normal mucous membrane is almost always sharp and usually at a 45 degree oblique, the superficial portion of the normal tissue leaning toward the neoplastic (Fig. 5). Sometimes small nodes of abnormal cells can be seen in the basal layer of the adjacent normal epithelium (Fig. 6). The basal layer of the intraepithelial lesion consists of more or less spindle shaped cells, which often show loss of polarity, arranged on the unbroken basement membrane. The underlying stroma shows a considerable infiltration with lymphocytes and a distinct vascular engorgement which may account for the pinkish color noted in these lesions on clinical examination (Fig. 7). Frequently it will be noted in sections, that the entire layer of abnormal covering epithelium has pulled free of the underlying stroma. This stripping phenomenon suggests that intraepithelial cancer possesses the same lack of adhesiveness that has been recently demonstrated for invasive epidermal and glandular cancer (8). This quality was recognized long ago by the Germans who compared this type of malignancy to the icing on a cake. One must bear it in mind in interpreting specimens from the operating room. Three of our specimens removed vaginally showed extensive raw surfaces with little evidence of the lesion (Figs. 8 and 9). Because of the ease with which positive biopsies were obtained beforehand, one must assume that the superficial layers were wiped off during the trauma of surgery. This quality suggests that small superficial lesions may be removed by curettage or destroyed by cauterization.

The extent of the lesion varies tremendously from a minute one occupying a small segment of the squamocolumnar junction at the external os (Fig. 10) to one which spreads entirely over the portio, even to the adjacent vagina, as noted by Younge and associates, and up the cervical canal almost to the internal os. Almost always the shape of the area is asymmetrical and rarely is it multicentric (Fig. 11). In all of our cases the mucosa at the external os was involved. In 2, the lesions were small and entirely superficial. In 1 of these it was probably entirely removed by the diagnostic biopsy. In 3, the exact extent of the lesion could not be determined, the portio having been wiped clean during the trauma of vaginal removal. The remaining 8 cases showed extensive involvement of the portio and also of the cervical canal. Replacement of the normal columnar

cells of the cervical glands by a layer or plug of neoplastic cells was noted in 10 of the 13 specimens (Fig. 12). However, in all of them the basement membrane about the glands appeared to be intact. In 7, this process was extensive, in some instances almost reaching the internal os (Fig. 13). Although TeLinde and Galvin have regarded this as a manifestation of invasion, most observers feel that it is merely an extension of the surface process since no stromal involvement can be demonstrated. One feels compelled to mention the 27 specimens studied most meticulously by Foote and Stewart in regard to the extent of the lesion; all but 2 were found to impinge on the external os; 14 involved both the portio and the canal, while 10 involved the portio alone; in 3, the canal alone was involved, and in only 1 of these was the lesion adjacent to the squamocolumnar junction. They observed a very high incidence of gland involvement.

TRANSITION TO INVASION

The transition to invasion obviously must take place at some point along the frequently extensive basement membrane, which lies between the superficial lesion and the underlying stroma. It was found at its earliest stage in one of our specimens. The neoplastic cells filling one of the cervical glands appear to be pouring through this break into the stroma, almost as if they were under pressure (Fig. 14). Since this area was deep in the canal, it is most doubtful that it could have been detected by any clinical measure. Two other specimens presented small but characteristic areas of well defined invasion. One of these was situated on the posterior lip of the cervix and was demonstrated preoperatively by wedge biopsy (Figs. 15 and 16). The other, situated high in the canal, was missed because of failure to use cervical curettage. It is believed that characteristic tissue could have been obtained from this case with a curette.

CLINICAL CHARACTERISTICS

Source. All of these patients did not come from the gynecological out-patient department or wards. Six were referred from other services in the hospital, some of them because of bleeding following bimanual examination. Two were referred because positive smears had been obtained outside of the hospital, in 1 instance by an internist. This variability of source brings out the fact that vigilance in the detection of these lesions must be exercised not only by the gynecologist, but by all physicians caring for adult women.

Age. The average age of the patients showing intraepithelial lesions was 40, slightly older than that found in other series (23, 24), but well below that of clinically recognizable invasive cancer of the cervix. The youngest was 27, the oldest 64. The women showing subclinical invasive lesions were 33, 37, and 55 years old.

Race. Ten of these patients were white, the remainder colored.

Parity. Thirteen had borne one or more term infants. Two had never been pregnant, one because her husband was totally sterile. One had been aborted twice.

Symptoms. Six patients gave a history of irregular or intermenstrual bleeding. In 2, this occurred after bimanual examination, in 1 it had occurred repeatedly after coitus. Among these cases were 2 of the 3 with preclinical invasion. The remainder had no symptoms referable to the cervix. One presented herself with a 7 year history of sterility, and one because she desired sterilization after having borne 7 living children. It cannot be emphasized too often that women over 30 who develop intermenstrual bleeding, particularly when related to trauma, are entitled to careful investigation of the cervix, both canal and portio, no matter how normal this organ may be to sight and touch. Two cases have been encountered in the past year which emphasize the importance of such investigation. One of them, a woman of 40 with fibroids, developed metrorrhagia in the summer of 1948. She was subjected to curettage in November, 1948. The pathologist noticed a small superficial strip showing epitheliomatous changes. Since the cervix grossly appeared perfectly normal, the gynecologist assumed this finding to be insignificant. Metrorrhagia continued and in February, 1949 a supracervical hysterectomy was performed. In April, 1949 a stage I carcinoma of the stump was discovered. The other, a 40 year old woman cared

for on the Bellevue Service, complained of metrorrhagia in 1947. A curettage showed nothing abnormal in the endometrium. Recent review of the section has shown no evidence of cervical carcinoma. She was admitted in the spring of 1949 with stage II cancer of the cervix. It is believed that careful study of both these cases at the time of the initial operative procedure by smears and biopsy would have revealed an intraepithelial or early invasive lesion. At the present time all patients on our service with metrorrhagia are being investigated by multiple cervical biopsies and cell smears as well as by curettage.

Associated pathology. Three of these patients had fibroid tumors, while three additional patients had been subjected to supracervical hysterectomy because of such tumors. One of the latter was performed in a private hospital after the intraepithelial lesion had been recognized at Bellevue. One had an extensive cystocele and rectocele, the cervical lesion being recognized by biopsy performed at the time of a plastic repair. One had a double uterus. The frequent presence of associated pathology should not blind one to the possible presence of early cervical cancer. The advantage of the more extensive use of total hysterectomy should be obvious.

Palpation and inspection of the cervix. The information to be gained in these cases by simple inspection and palpation of the cervix has already been summarized under gross pathology. With one exception, the patient exhibiting a small papillomatous mass, there was no suggestion of the presence of a malignant tumor. In 5, the so called erosion was noted, while in the remainder nothing was found except for small well healed lacerations, which did not seem to demand treatment. In order to detect these subclinical lesions, we must depend on two aids in diagnosis. The first, long utilized, is biopsy; the second, and more recent, is the cell smear.

BIOPSY

Biopsy applied to the preclinical lesion, must be used in a different manner than in clinically obvious cancer. In the latter, the area from which tissue must be obtained can be selected. In the former the lesion can neither be seen nor felt, and the procedure is, therefore, a random one. The one advantage lies in the fact that almost all of these lesions are related to the external os. Obviously, since the lesion may be small, and is usually asymmetrical, multiple biopsies will be more likely than single ones to reveal it. Foote and Stewart came to interesting conclusions in their careful study of 27 specimens. Thirteen of these could have been recognized by pieces removed from the anterior lip, 13 if taken from the posterior lip, 20 by pieces removed from both these areas, and 25 with pieces removed from both lateral quadrants as well. In the 2 remaining cases, biopsy seemed doomed to failure because the lesion was situated above the external os in the cervical canal. In order to obviate such difficulties, Novak has devised a spoon by which the whole squamocolumnar junction can be scraped off for examination; Gusberg (5) has designed a special instrument to remove the squamocolumnar junction; Ayre has designed a special double edged knife set at 45 degrees with its handle to excise the margin of the external os; while Gladstone has developed the gelatin sponge biopsy.

All of these newer methods suffer from the fact that insufficient amounts of underlying stroma, to rule out invasion, are removed, and because the small pieces are often difficult to orient in order to obtain a section vertical to the surface. Furthermore, it must be remembered that deep excision of the squamocolumnar junction may lead to stricture, a complication not to be belittled when one takes into account that the bulk of these patients are found to be innocent of neoplasm. For these reasons we have preferred to take biopsy specimens from 4 quadrants of the external os, using a square nosed sharp Schubert punch, similar to that recommended by Younge and associates. The piece obtained can be readily oriented and contains abundant underlying stroma. The possibility of subsequent stricture is minimized, because ample intervening tissue is left. One must remember that a supposed intraepithelial lesion found in biopsy may be the margin of an invasive cancer, and the cervical canal should be carefully curetted to rule out such a possibility.

While this procedure can be carried out in the office, the bleeding being controlled by oxidized gauze and the pressure of a tampon, in many instances bleeding requires further control by suture. Such incidents make the hospitalization of patients subjected to this diagnostic procedure desirable.

Positive biopsies have been obtained preoperatively in 15 of the 16 patients utilized in this report. The 16th, a patient who requested sterilization because of 7 living children, was subjected to total hysterectomy, after multiple negative biopsies, because of several positive cell smears. A small lesion at about 2 o'clock was found on the squamocolumnar junction in the specimen removed at operation. In another case, invasion was recognized in the posterior lip, although the lesion in the anterior lip appeared to be confined to the surface. In another, invasion was missed through failure to curette the cervical canal. Our only serious error arose from a similar omission in a patient discovered, during operation, to have an advanced carcinoma of the cervical canal. Her case has not been included in the material discussed in this paper. The remaining case, with preclinical invasion, was so early that it probably could not have been detected by curettage. Random biopsy yielding pieces of tissue capable of proper orientation has, therefore, given us most efficient results.

CELL SMEARS

While Schiller (18) called attention to the importance of examining scrapings of the cervix in arriving at a diagnosis, this type of procedure has been brought to recent popularity by the work of Papanicolaou and Traut. They originally aspirated material from the vault of the vagina and the cervical canal, in the knowledge that malignant cells exfoliate from the surface of early, and otherwise undetectable neoplasms. Since such material was obtained indirectly and mixed with large quantities of normal cells, which undergo similar but possibly slower exfoliation, certain disadvantages soon became obvious. Because of the paucity of malignant cells, the reading of such smears was time-consuming and difficult. The site of the tumor of origin might lie anywhere between the cervix and the ovary. When a malignant ovarian tumor exfoliates, it may be presumed to have already become metastatic; tubal carcinoma is rare; carcinoma of the fundus, with few exceptions, can be more readily recognized by curettage. The important area of application of the cell smear is the cervix, from which material can be taken directly, some form of instrument being used to scrape the portio, particularly in the region of the external os. Ayre has devised a wooden spatula; Myller a metal cone from the sides of which two shallow sharp wings project in the vertical axis. After a short trial with the aspiration technique, Ayre's wooden spatula was adopted at Bellevue Hospital to obtain cell smears directly from the cervix. The preparations obtained by it were greatly improved and much easier to read and interpret.

Of the 16 cases forming the basis of this report, smears were not obtained in the 3 earliest instances. In the 13 remaining, 11 were regarded as positive. Of the balance, 1 was said to contain atypical cells, and was obtained from a patient in whom all, or most of the lesion was removed by a previous biopsy. In the other, the preparation was poorly stained and was said to be unsatisfactory. This smear was recently restained and appears to be definitely positive. In positive smears, cells are found singly, or in groups, whose appearance carry the same stigma of malignancy already mentioned under microscopic pathology. It would be repetitious to describe their character (Figs. 17–24). It can be stated, therefore, that this method has given us positive results in every case in which it was utilized, except in one in whom its failure can be readily explained. Its chief advantage lies in the fact that it should pick up even the smallest lesions provided that they are not located high in the canal; that it is easy to apply; and that it does not require hospitalization. Its chief disadvantage lies in the time required for proper study of each slide, and the essential need for training and experience in the interpretation of the findings. The trained pathologist should acquire the ability to read such smears in short order. It is a much more difficult matter to train the technician who must sift the large majority

of normal smears from the abnormal. This is the real shortage at present. The development of personnel, techniques, and special laboratories to carry out cytological studies on large numbers of women, holds great hope for the future. The pessimism expressed by some in regard to this technique, because of expense, wastage of time, lack of personnel, etc. is unjustified. If some of the vast sums devoted to irrelevant cancer research were set at work in this field, progress might be accelerated. Certainly it is not a method of diagnosis, but a means to select patients for careful study of biopsy and curettage.

A personal reaction may be expressed against the present cumbersome classification, under which smears are often reported. Many use five groups, at one extreme being definite malignancy, at the other, normal, while in between are those ranging from atypical to suspicious. It is believed that the sooner we become able to grade such smears as positive, or negative, and to reduce the doubtful reports to a tiny minimum, the more value they will become clinically, and the less disturbing to the patient. It is believed that this will come to pass since today most atypical and suspicious smears result in the obtaining of biopsies innocent of malignant change.

SUMMARY AND CONCLUSIONS

Since April, 1947, sixteen cases of preclinical carcinoma of the cervix have been discovered at Bellevue Hospital; 13 were intraepithelial, 3 early invasive tumors. The pathology has been reviewed, and certain features pointed out which are of value in their recognition.

The clinical details and the gross appearance of the cervix in these patients has been summarized. The importance of metrorrhagia as a symptom has been stressed.

The prime importance of random biopsy and of cell smears in arriving at a diagnosis has been brought out. These diagnostic aids reinforce each other and must be used together.

The means by which well defined early invasion can be discovered in most instances has been described.

It is believed that knowledge of the lesion, the use of smears to detect their presence, and of biopsy and curettage to define their character and extent, should, when applied on a large scale, change greatly the present day end results of carcinoma of the cervix.

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INFLUENCE OF ANTIBIOTICS AND SULFONAMIDES ON THE MORTALITY AND BACTERIA OF EXPERIMENTAL PERITONITIS

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IT is now agreed that the use of the sulfonamides and the antibiotics has been associated with a substantial reduction in the morbidity and mortality of patients with peritonitis. Yet it is difficult to evaluate the exact role these chemotherapeutic agents have played in the recovery of such patients. Evaluation is difficult because of the many variables which play a part in the development of peritoneal infection and the many variables which are concerned with recovery from peritoneal infection. Such variables encountered clinically include (1) etiology, i.e. appendicitis, diverticulitis, etc., (2) resistance of the individual patient, (3) the time interval between development of the disease and the institution of therapy, (4) anesthetic management, and (5) supportive therapy including fluids, electrolytes, caloric intake, whole blood, intestinal decompression, and other measures.

Although a great deal has been learned regarding the pathologic physiology of peritonitis within recent years, little is known of the exact mechanism or mechanisms which lead to death. Various bacterial organisms multiply in the peritoneal cavity, and it has been assumed that these bacteria liberate toxins which produce adverse local and systemic effects. Although specific types of bacteria—Escherichia coli, Clostridia welchii, and streptococci—have been incriminated as the organism chiefly responsible for the adverse effects of peritonitis, there is no agreement as to whether one specific bacterial organism or groups of symbiotic bacteria are responsible for the morbidity associated with peritonitis. Furthermore, there is no indication as to whether the adverse effects of bacterial peritonitis are due primarily to bacterial toxins liberated within the peritoneal cavity, to bacterial invasion of the tissues surrounding the peritoneal layer, to bacterial invasion of the lymphatic and blood streams, or to combinations of these factors.

It is of considerable interest that the morbidity and mortality of peritonitis have been favorably influenced by penicillin therapy in spite of the fact that many of the bacteria most frequently found in this type of polymicrobic infection are not susceptible to the action of penicillin in vitro. Crile has postulated that the gram positive cocci are the chief offenders in peritonitis and that once they are controlled the gram negative organisms are controlled by the defense mechanism of the body.

Because streptomycin is generally effective in the treatment of many infections due to organisms not susceptible to the action of penicillin, considerable interest had been aroused regarding the treatment of polymicrobic peritoneal infections with this antibiotic. In the experience of a number of investigators (2, 4, 6, 9), streptomycin therapy alone has prolonged the survival time or increased the survival rate of animals with experimentally produced peritonitis. However, streptomycin has been less effective than was originally hoped and less than might have been expected on the basis of in vitro sensitivities of organisms commonly found in peritonitis.

The purpose of this investigation was to determine the relative effectiveness of penicillin and streptomycin and combinations of penicillin, streptomycin, and sulfonamides in the treatment of experimentally produced peritonitis in dogs which received no other

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type of specific or supportive therapy. These findings were to be correlated with qualitative bacteriological studies including the antibiotic sensitivities of the bacterial organisms recovered both initially (at the time of the operative production of peritonitis) and terminally (at the time of death or sacrifice of the dogs).

EXPERIMENTAL METHODS

Mongrel dogs of both sexes weighing from 7.7 to 16.0 kilograms were used. The average weight of the dogs was 9.3 kilograms. Water but no food was allowed the dogs during the 24 hours preceding operation. Anesthesia was produced by the intravenous injection of 0.4 cubic centimeter of a 6 per cent solution of sodium nembutal per kilogram of body weight. With the observance of aseptic precautions, the abdomen was opened through a midline incision. After delivery of the appendix, the lateral vessels of the appendix and the mesoappendix were divided and ligated. The base of the appendix was ligated with a single strand of umbilical tape at the level of the cecal wall. The lumen of the appendix was opened by a longitudinal incision from the tip of the appendix to approximately 1.0 centimeter from the umbilical tape ligature (Fig. 1) at the base of the appendix. A specimen for the initial bacteriological studies of the appendiceal contents was taken with a cotton swab. The tip of the opened appendix was then grasped with an Allis forceps and after the opened avascularized appendix was returned to the peritoneal cavity, the appendix was passed between the abdominal viscera and the parietal peritoneum in an arc starting in the left upper quadrant, passing through the left side and ending in the right lower quadrant (Fig. 1). Following closure of the abdominal wall in layers with silk sutures, the dogs were given 55 cubic centimeters of castor oil by stomach tube. The conditions thus produced were ideal for the development of a widespread polymicrobic peritonitis.

Water was allowed the dogs as soon as they recovered from the effects of the operation and anesthesia. Food was offered to the dogs 24 hours after operation. Those that survived for more than 10 hours uniformly developed marked distention of the abdomen and other classical signs of widespread peritoneal infection. All dogs which died within 10 days were subjected to autopsy immediately after death. All the dogs that lived for 10 days were sacrificed on the tenth postoperative day with the exception of 6 dogs treated with penicillin.

Peritonitis was produced, by the method described, in 107 dogs. Group I, the control group, consisted of 27 dogs which received no sulfonamide or antibiotic therapy. The 20 dogs of group II received both penicillin and streptomycin hydrochloride parenterally. The 15 dogs of group III had sulfanilamide crystals implanted locally in the peritoneal cavity at the time of operation and then received penicillin, streptomycin, and sodium sulfadiazine parenterally. Group V, which consisted of 15 dogs, received only parenteral streptomycin and group VI, which consisted of 15 dogs, received only parenteral penicillin therapy.

CHEMOTHERAPY

All antibiotic therapy was begun immediately after operation and continued until the dogs died or until the expiration of the 10 day postoperative period of observation. Penicillin, 60,000 units in beeswax and oil, was administered intramuscularly every 12 hours. Streptomycin was administered in doses equivalent to 16.6 micrograms per kilogram of body weight, every 4 hours. When sulfonamides were used, 0.4 of a gram of sulfanilamide crystals was implanted in the peritoneal cavity in the area of the appendix at the time of operation and sodium sulfadiazine, 0.325 gram in 6.5 cubic centimeters of aqueous solution was injected intravenously every 12 hours.

The terminal bacteriological cultures of the peritoneal cavity were taken of that portion of the peritoneal cavity which grossly exhibited the most severe pathological changes at the time of death or sacrifice. The various types of bacterial organisms were determined in the dogs of group III (penicillin, sulfonamides and streptomycin); group IV (penicillin and sulfonamides); and group V (streptomycin). In group VI (penicillin) and group II (penicillin and streptomycin), the number of

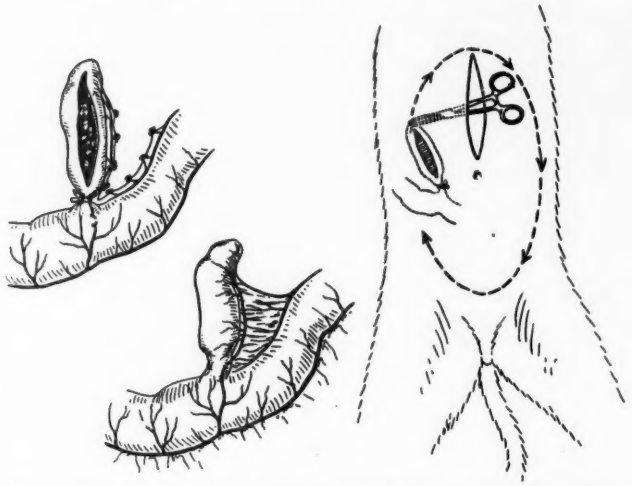

Fig. 1. Diagrammatic representation of the ligation of appendiceal vessels, division of mesoappendix, ligation of appendiceal base, incision of the appendix, and the method of contamination of the peritoneal cavity.

individual bacterial strains was determined. In the control group (group I) the types of bacteria present were determined in 21 dogs and the number of individual strains of bacteria was determined in 10 of the 27 dogs.

The penicillin sensitivities of the strains of bacteria recovered from the dogs, initially and terminally, were determined in group II (penicillin and streptomycin) and group VI (penicillin). The streptomycin sensitivities of the strains of bacteria obtained from the dogs of group II (penicillin and streptomycin) were also determined. The penicillin sensitivities were determined by the Rammelkamp serial dilution method (5). The streptomycin sensitivities were determined by a serial dilution method (7). When more than one strain of the same type of organism was present in a single culture specimen, the sensitivity showing the highest resistance to penicillin or streptomycin has been used in the tabulations. Organisms were arbitrarily designated as sensitive to penicillin, when they were inhibited by 0.5 or less of a unit of penicillin per cubic centimeter of culture medium. Organisms were considered sensitive to streptomycin when their growth was inhibited by 10 micrograms or less of streptomycin per cubic centimeter of culture media.

RESULTS

Mortality. The survival rates of the various groups of dogs are shown graphically in Figure 2. Only one of the 27 untreated dogs survived the 10 day period of observation, a survival rate of 3.7 per cent. The lone surviving dog of the group had developed a fistula which opened on the abdominal wall. Of the dogs treated with penicillin and sulfonamides, 40 per cent survived. Of the animals treated with penicillin, streptomycin, and sodium sulfadiazine systemically and sulfanilamide in the peritoneal cavity, 60 per cent survived. With a combination of penicillin and streptomycin, 60 per cent survived. With systemic streptomycin therapy alone only 27 per cent survived. However, with systemic penicillin therapy alone, 66 per cent of the dogs survived.

No greater incidence of adhesions was noted in the groups of dogs which received intraperitoneal sulfanilamide. In all the groups of dogs, adhesions were frequently found after 154 hours but usually only in the vicinity of the necrotic appendiceal tissue. All of the dogs which died within 154 hours of the time of operation showed diffuse purulent peritonitis at autopsy. After 154 hours some of the dogs had an abscess or the beginning of abscess formation.

Bacteriology. The average number of initial and terminal types and strains of bacteria per dog are tabulated in Table I. There was no marked difference in the initial number of bacterial types present in any of the groups of dogs. Likewise there was no consistent difference between the number of types of organism present initially in the animals that lived and those that died in any given group. Death or survival of animals within any given group therefore could not have been predicted on the basis of the average number of bacterial types present on initial culture.

The average number of bacterial types present terminally in group IV (penicillin and sulfonamides) and group V (streptomycin) was lower than in the other groups. However, this low incidence of bacterial types was not associated with a lowered mortality in these groups. The mortality of the dogs in group V was the highest of all the treated experimental groups. Survival or failure to survive could not be explained by the total number of bacterial types present in the terminal cultures.

There was a smaller number of initial *strains* of bacteria found in group VI (penicillin) than was found in group I (controls) and group II (streptomycin and penicillin). The number of bacterial strains was not determined in the other experimental groups.

We found, as have others, Lockwood (3), bacterial types present in the terminal cultures which were not present in the initial cultures of the same dogs. The total number of bacterial organisms which appeared for the first time in the terminal cultures of group I (controls) and group VI (penicillin) are shown in Table II. Previously unidentified bacterial organisms appeared both in dogs that died and those that were sacrificed. Aspiration of peritoneal fluid at 32½ and 40 hours after operation in 2 dogs of group IV (penicillin, streptomycin, and sulfonamides) also demonstrated bacterial organisms not found in the appendix at the time of operation. Cultures of the operative wounds in 20 dogs immediately before closure of these wounds, failed to show any correlation between the bacterial flora of the wounds and the new bacteria which appeared in the peritoneal cavity after operation had been performed.

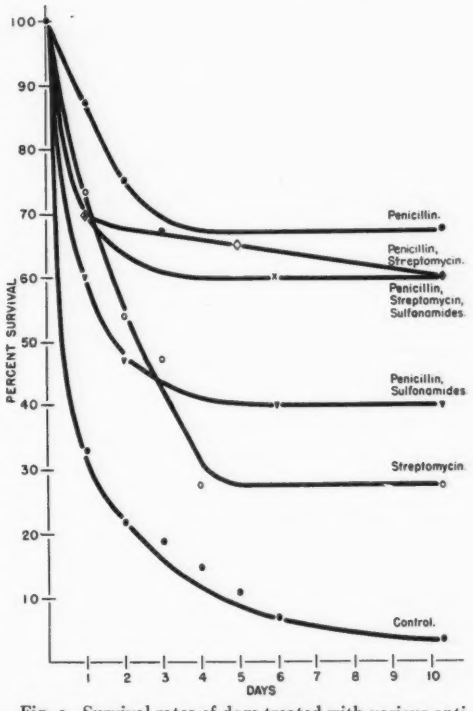

Fig. 2. Survival rates of dogs treated with various antibacterial agents and combinations of antibacterial agents during the 10 days of treatment after the experimental production of peritonitis.

From the initial bacteriological data obtained it was not possible to designate one specific bacterial organism (Table III) or a combination of the three most commonly found organisms, Escherichia coli, streptococci, and clostridia, as being responsible for the virulence of the disease (Table IV). Similarly an analysis of the incidence of these same organisms in the terminal cultures failed to show any significant relationship to the death or survival of the animals (Table V). This is in agreement with the findings of Kay and Lockwood (3) who could not correlate the bacterial types found with mortality. They found that pathogens occurred with almost equal frequency in the exudates of the animals which survived and those which succumbed. Table III lists the incidence of the 9 most commonly found organisms in the initial cultures in respect to death or survival of the

TABLE I.—AVERAGE NUMBER OF INITIAL AND TERMINAL BACTERIAL TYPES AND STRAINS PER DOG

Group	Survival	Initial culture		Terminal culture	
		Types	Strains	Types	Strains
Group I—controls	Died	3.17*	5.4†	2.53*	3.89†
	Sacrificed				
	Total group	3.17*	5.4†	2.53*	3.89†
Group II—streptomycin and penicillin	Died	3.12	5.75	3.62	5.00
	Sacrificed	2.85	3.75	2.86	4.85
	Total group	2.87	4.79	3.27	4.93
Group III—streptomycin, penicillin, and sulfonamides	Died	3.17		2.83	
	Sacrificed	3.22		3.33	
	Total group	3.20		3.08	
Group IV—penicillin and sulfonamides	Died	2.78		1.75	
	Sacrificed	2.17		1.40	
	Total group	2.53		1.56	
Group V—streptomycin	Died	3.00		1.50	
	Sacrificed	2.66		1.67	
	Total group	2.92		1.54	
Group VI—penicillin	Died	3.00	3.20	1.20	1.20
	Sacrificed	2.90	3.50	3.33	4.22
	Total group	2.93	3.40	2.57	3.07
All groups	Died	3.08		2.22	
	Sacrificed	2.98		2.70	
	Total	2.96		2.63	

*Twenty-one of the 27 dogs in this group.
†Ten of the 27 dogs in this group.

animals in each group. In the initial cultures of all of the dogs, Escherichia coli was found in 83 per cent, streptococci in 68 per cent, clostridia in 39 per cent and Bacillus proteus in 36 per cent. The incidence of the various types of bacteria in the initial cultures listed in Table III are remarkably similar in the dogs that lived and the dogs that died.

At the time of autopsy of the dogs 3 different types of peritoneal reaction were observed: (1) inflammation of part or all of the peritoneal cavity without abscess formation; (2) localized abscess or abscesses; and (3) no gross peritoneal reaction or exudate. The number of types of bacteria recovered terminally from the 3 different types of peritoneal reaction, curiously enough, was very similar both in the dogs that died and in those that recovered.

TABLE II.—TOTAL NUMBER OF BACTERIAL ORGANISMS APPEARING FIRST IN TERMINAL CULTURES, GROUPS I AND VI

Dogs	Number of bacterial types			New bacterial types found
	Initial culture	Final culture	Number of new bacteria	
Group I—10 dogs	58	43	8	Streptococci—1 Clostridia—2 Staphylococci—4 Proteus—1
Group VI—(penicillin lived)—10 dogs	28	30	8	Coli—1 Streptococci—2 Clostridia—1 Staphylococcus—1 Proteus—1 Diphtheroid—1 Salmonella—1
Group VI—(penicillin died)—5 dogs	15	5	2	Clostridia—2

Antibiotic sensitivities. The incidence of penicillin sensitive and penicillin resistant organisms in both the initial and terminal cultures of group VI (penicillin) are shown in Table VI. Of the initial cultures there was a higher incidence of penicillin resistant Escherichia coli in the dogs that died than in those that lived. The terminal cultures showed approximately an equal number of resistant Escherichia coli in the dogs that lived and those that died. There was also a higher incidence of penicillin resistant streptococcal organisms in the initial cultures of dogs that died. No penicillin resistant streptococci were found, however, in the terminal cultures of the dogs that died, whereas 30 per cent of the dogs that lived had penicillin resistant streptococci. Resistant clostridia were present in equal numbers in the terminal cultures of the dogs that lived and those that died. Penicillin sensitive organisms were frequently found in the dogs that survived the 10 day period of penicillin therapy.

The percentage incidence of penicillin and streptomycin sensitive and penicillin and streptomycin resistant organisms present in the initial and terminal cultures of group II (penicillin-streptomycin) are shown in Table VII. The dogs that died in group II showed a higher incidence of resistant Escherichia coli and streptococci than the dogs that lived, both on initial and terminal culture. Penicillin and streptomycin sensitive organisms were found in the cultures of the dogs that died as well as

TABLE III.—INCIDENCE OF BACTERIAL TYPES IN INITIAL CULTURES

Group	Therapy	Dogs	Incidence in per cent												
			Total coli	Hemolytic coli	Non hemolytic coli	Total streptococci	Hemolytic streptococci	Non hemolytic streptococci	Clostridia	Proteus	Diphtheroids	Staphylococcus	Salmonella	Pseudomonas	Prodigiosus
I	None	All	95	—	—	58	—	—	32	37	16	11	0	11	0
		Died	95	—	—	56	—	—	33	39	17	11	0	11	0
		Lived*	100	—	—	100	—	—	0	0	0	0	0	0	0
II	Penicillin and streptomycin	All	75	75	15	80	20	65	35	20	10	10	10	10	5
		Died	88	88	13	88	25	63	25	25	13	13	25	0	13
		Lived	67	67	17	75	17	67	42	17	8	8	0	17	0
III	Penicillin, streptomycin, and sulfonamides	All	100	—	—	100	—	—	7	93	13	0	0	0	0
		Died	100	—	—	100	—	—	17	83	17	0	0	0	0
		Lived	100	—	—	100	—	—	0	100	11	0	0	0	0
IV	Penicillin and sulfonamides	All	80	—	—	33	—	—	53	33	0	13	0	7	0
		Died	78	—	—	33	—	—	56	22	0	22	0	11	0
		Lived	83	—	—	33	—	—	33	50	0	0	0	0	0
V	Streptomycin	All	62	—	—	54	—	—	46	23	8	46	0	0	0
		Died	60	—	—	60	—	—	50	20	10	50	0	0	0
		Lived	67	—	—	33	—	—	33	33	0	33	0	0	0
VI	Penicillin	All	87	87	13	73	47	40	67	20	0	7	27	0	0
		Died	100	100	0	80	60	40	60	20	0	0	20	0	0
		Lived	80	80	20	70	40	40	70	20	0	10	30	0	0
All groups		All	83	—	—	68	—	—	39	36	9	14	6	5	1
		Died	86	—	—	65	—	—	40	34	11	18	6	5	1
		Lived	78	—	—	72	—	—	38	40	5	7	8	5	0

*Only 1 dog survived.

TABLE IV.—MORTALITY IN PER CENT OF DOGS WITH ONE OR MORE OF THE ORGANISMS, ESCHERICHIA COLI, STREPTOCOCCI, AND CLOSTRIDIA PRESENT IN INITIAL CULTURE (NUMBER OF DOGS IN PARENTHESES)

o—organism not present x—organism present			I Controls	II Penicillin, streptomycin	III Penicillin, streptomycin, sulfonamides	IV Penicillin, sulfonamides	V Streptomycin	VI Penicillin	All groups
Escherichia coli	Streptococci	Clostridia							
x	o	o	100(7)	50(2)	—(0)	50(4)	50(2)	50(2)	71(17)
o	x	o	—(0)	50(2)	—(0)	100(1)	100(1)	100(1)	80(5)
o	o	x	—(0)	—(0)	—(0)	50(2)	—(0)	—(0)	50(2)
x	x	o	75(4)	50(8)	45(11)	50(2)	100(2)	100(1)	57(28)
o	x	x	—(0)	0(1)	—(0)	—(0)	100(1)	0-(1)	33(3)
x	o	x	—(0)	0(1)	—(0)	100(3)	—(0)	0(1)	60(5)
x	x	x	100(6)	50(4)	100(1)	50(2)	67(3)	63(8)	60(25)

in the dogs that survived the 10 day period of penicillin and streptomycin therapy. The ratio of the number of penicillin and streptomycin sensitive to the number of resistant organisms present in the dogs of group II (penicillin and streptomycin) and group VI (penicillin) are given in Table VIII.

Antibiotic serum levels. The dogs that had only penicillin therapy had maximum serum penicillin levels which varied between 0.15 and

TABLE V.—MORTALITY IN PER CENT OF DOGS WITH ONE OR MORE OF THE ORGANISMS: ESCHERICHIA COLI, STREPTOCOCCI, AND CLOSTRIDIA IN TERMINAL CULTURE (NUMBER OF DOGS IN PARENTHESES)

x—organism present			I Controls	II Penicillin, streptomycin	III Penicillin, streptomycin, sulfonamides	IV Penicillin, sulfonamides	V Streptomycin	VI Penicillin	All groups
Escherichia coli	Strepto-coccus	Clostridia							
x	o	o	100(7)	50(2)	0(1)	—(0)	0(1)	75(4)	73(15)
o	x	o	—(0)	0(1)	—(0)	—(0)	100(1)	0(1)	33(3)
o	o	x	100(2)	—(0)	—(0)	—(0)	—(0)	100(2)	100(4)
x	x	o	100(5)	38(8)	67(6)	50(2)	100(1)	0(2)	55(22)
o	x	x	—(0)	—(0)	—(0)	—(0)	—(0)	0(1)	0(1)
x	o	x	100(2)	—(0)	—(0)	—(0)	100(1)	—(0)	100(3)
x	x	x	100(2)	100(4)	25(4)	—(0)	100(1)	0(4)	53(15)

1.3 units of penicillin per cubic centimeter of serum, 6 to 12 hours after an injection. The average maximum penicillin serum level in these dogs was 0.23 units 12 hours after injection. In group V (streptomycin) the average streptomycin serum level was approximately 30 units 1 hour after injection, and 22 units 4 hours after injection. No sulfonamide serum levels were determined.

DISCUSSION

These experiments were undertaken with the object of performing as complete a bacteriological study as possible of bacteria of the peritoneal cavity in dogs with experimental peritonitis as well as to determine the effectiveness of the chemotherapeutic agents used. Initially it was presumed that we would find that the organisms sensitive to the chemotherapeutic agents would disappear from the peritoneal cavity in those animals which were to survive. The persistence of sensitive bacterial organisms in the dogs that survived the 10 day period of observation probably was due to their survival in the necrotic appendiceal

TABLE VI.—INITIAL AND TERMINAL INCIDENCE IN PER CENT OF PENICILLIN SENSITIVE AND PENICILLIN RESISTANT BACTERIAL TYPES IN DOGS TREATED WITH PENICILLIN

Bacterial organisms	R=Resistant S=Sensitive	Initial cultures		Terminal cultures	
		Lived	Died	Lived	Died
Escherichia coli	R	80	100	70	60
	S	0	0	0	0
Streptococci	R	30	60	30	0
	S	30	20	10	0
Clostridia	R	70	60	40	40
	S	0	0	10	0
Proteus	R	10	0	0	0
	S	0	0	0	0
Diphtheroids	R	0	0	0	0
	S	0	0	10	0
Staphylococci	R	0	0	0	0
	S	10	0	0	0
Other organisms	R	40	20	40	0
	S	0	0	0	0

TABLE VII.—INITIAL AND TERMINAL INCIDENCE IN PER CENT OF PENICILLIN OR STREPTOMYCIN SENSITIVE AND RESISTANT BACTERIAL TYPES IN DOGS TREATED WITH PENICILLIN AND STREPTOMYCIN

Bacterial organisms	R=Resistant S=Sensitive	Initial cultures		Terminal cultures	
		Lived	Died	Lived	Died
Escherichia coli	R	36	63	43	88
	S	45	25	29	13
Streptococci	R	55	88	71	88
	S	36	0	0	0
Clostridia	R	27	0	0	25
	S	18	25	0	0
Proteus	R	18	13	0	0
	S	0	0	0	0
Diphtheroids	R	0	0	0	0
	S	9	13	29	25
Staphylococci	R	0	0	14	13
	S	0	13	43	38
Other organisms	R	27	50	14	50
	S	27	0	43	38

TABLE VIII.—EXPERIMENTAL PERITONITIS RATIO OF SENSITIVE TO RESISTANT ORGANISMS

Group	Therapy	Dogs	Initial cultures		Final cultures	
			Penicillin S/R	Streptomycin S/R	Penicillin S/R	Streptomycin S/R
II	Streptomycin and penicillin	All	0.125	0.088	0.250	0.622
		Died	0.091	0.333	0.227	0.333
		Lived	0.154	0.790	0.357	1.375
VI	Penicillin	All	0.143	——	0.125	——
		Died	0.083	——	0/5	——
		Lived	0.174	——	0.167	——

tissues and in abscess cavities surrounding the necrotic appendiceal tissues, although in a number of instances sensitive bacteria were found on grossly normal peritoneal surfaces. It is well recognized that antibiotic agents and sulfonamides do not usually sterilize the contents of an abscess cavity because of failure of these substances to gain entrance into such cavities. Sensitive organisms probably flourish in necrotic appendiceal tissue for the same reason—namely, lack of blood supply and lack of diffusion of chemotherapeutic agents into the tissue.

The data obtained do not explain why penicillin therapy alone was as effective or slightly more effective than a combination of streptomycin and penicillin or the combination of streptomycin, penicillin, and sulfonamides. The fact that penicillin was as effective as the two combinations mentioned could be interpreted as suggesting that penicillin sensitive organisms were the pathogenic organisms in peritonitis and that the penicillin resistant organisms existed in the peritoneal cavity as saprophytes or were pathogenic only in symbiosis with penicillin sensitive organisms. Penicillin may have partially inhibited the growth of penicillin sensitive organisms in the general peritoneal cavity and reduced the degree of bacteriemia of penicillin sensitive organisms while those same organisms may have flourished in the necrotic appendiceal tissue (which was frequently the site cultured terminally). It can be stated, however, that the average penicillin sensitivities of the various organisms usually considered to be sensitive to the action of penicillin, was not significantly different in the dogs that lived than in the dogs that died either on initial or terminal cultures.

In other work carried on concurrently with the present study, investigations were made of the rate of degree of spread of bacteria within the peritoneal cavity, the bacterial invasion of tissues adjacent to the parietal peritoneum in the presence of peritonitis (10), and the bacteriemia associated with peritonitis and the effect of penicillin on this bacteriemia (8).

Other variables which were considered as possible factors in the survival or death of the dogs were breed of dog, distemper, sex, relative weight, secondary pneumonia, intestinal parasites, and length of stay in the animal house before operation. None of these variables were found to be significant. Preoperatively all of the dogs of group VI and 10 dogs each of groups I and II received distemper vaccine of the Green type as well as therapy for the specific types of intestinal parasites present in each individual dog. The mortality of the dogs of groups I and II which received distemper vaccine and therapy for parasites did not differ from that of the other dogs, which did not receive such preoperative therapy.

CONCLUSIONS

1. Penicillin therapy alone over a period of 10 days was as effective as a combination of penicillin and streptomycin or a combination of penicillin, streptomycin, and sulfonamides in the treatment of experimentally produced peritonitis in dogs.

2. Streptomycin alone did produce a decreased mortality as compared to the control dogs; however, the results were definitely inferior to those with penicillin alone, with a combination of penicillin and streptomycin, or with a combination of penicillin, streptomycin, and sulfonamides.

3. Death or survival of the dogs in any given group could not be correlated with a difference in the initial or terminal number of bacterial types or strains present in the peritoneal cavity.

4. Frequently new forms of bacteria which were not present in the initial cultures of the peritoneal cavity were found on terminal cultures.

5. From the available bacteriological data it was not possible to designate one bacterial organism or any combination of the three most commonly encountered bacterial organisms (Escherichia coli, streptococci, and clostridia) as being responsible for the mortality of the peritonitis in these dogs.

6. Of the 6 most commonly found bacterial organisms it was not possible to predict the result of penicillin or penicillin and streptomycin therapy on the basis of the antibiotic sensitivities of the bacterial organisms found in the initial cultures.

7. Bacterial organisms sensitive to the antibiotics used for treatment, were frequently found in the peritoneal cavity on terminal culture both in the animals that lived and those that died.

8. Preoperative treatment with distemper vaccine and specific therapy for intestinal parasites did not alter the mortality of experimentally produced peritonitis.

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RADICAL TREATMENT OF CARCINOMA OF THE PROSTATE GLAND BY CYSTOVESICULOPROSTATECTOMY

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THE radical operation for cancer of the prostate has hitherto practically always been performed by perineal extirpation after the method of Young, with or without minor modifications. That perineal extirpation has not become more popular is due to the high incidence of recurrence and the not uncommon postoperative permanent urinary incontinence, a complication the patient should be spared if possible. The method has been practically abandoned by most Scandinavian surgeons; for example, according to Abrahamsen, perineal prostatectomy was used in only 1 of 730 cases of cancer of the prostate treated in Denmark during the years 1941 to 1945. At the Caroline Hospital, Stockholm, during the period 1940 to 1946 perineal prostatectomy was performed in only 4 of 200 patients. In at least 2 of these 4 patients urinary incontinence persisted after operation. Stein Holst, of Oslo, has treated 188 patients with cancer of the prostate, but in none of them did he perform perineal prostatectomy. During the years 1939 to 1948 in all some 370 patients with cancer of the prostate were treated at the surgical clinics of the Sahlgren Hospital, but perineal prostatectomy was not used in a single instance. The procedures carried out in these cases were: suprapubic prostatectomy in 62 cases (the preoperative diagnosis in most of them was hypertrophy), electroresection in 100 cases, and castration in 78.

After a diagnosis of cancer of the prostate has been provisionally established, most Swedish surgeons content themselves with verification of the diagnosis and the improvement of the urinary passage, by electroresection, followed by the use of hormone therapy, sometimes in combination with castration. While this treatment is only palliative—it causes the symptoms to subside and the general condition of the patient to improve, and it may prolong life for some years—it is by no means a very satisfactory prognosis to offer to patients, especially if they are young or middle-aged. Therefore I have long since desired to devise a radical operative method that will promise more permanent results and insure less risk of urinary incontinence than does the Young method. The retropubic extirpation of the prostate and the seminal vesicles suggested by Millin but hitherto used in only a few cases offers a much better survey of the operative field than does the perineal operation, but it does not eliminate the risk of urinary incontinence. Millin himself is of the opinion that the danger of incontinence is slight unless the cancer has overgrown the apex of the prostate. When the method of Millin is used there is always the danger that the operator, for fear of injuring the sphincter, will not always perform a sufficiently radical operation, and the disease will then recur.

Since, in the treatment of cancer of the bladder, total extirpation of the urinary bladder with transplantation of the ureters into the colon has become a fairly common operation and its mortality is moderate, one is tempted to employ this operation in the treatment of primary prostatic cancer. This is especially true since even in cases of cancer of the bladder the bladder is generally extirpated together with the prostate and seminal vesicles in order to insure radical removal of the lesion. Judging by the literature, however, no authors have—on the basis of experience—recommended this type of operation for localized, primary, prostatic cancer. Ritter (1947) and Giertz (1948) mention the possibility of this radical procedure for cancer of the prostate, but they themselves have not tried the operation, nor do they express an opinion as to its suitability.

The only traceable case in the literature in which the bladder and the seminal vesicles

From the Surgical Clinic II of the Sahlgren Hospital, Gothenburg.

and the prostate were extirpated in the treatment of localized, prostatic cancer is the one operated upon by Coffey (1931). In 1933 he reports 11 cases of cystectomy for carcinoma of the bladder (4). A perusal of these case reports showed that in 1 patient there was no cancer of the bladder but that the diagnosis before the operation was "cancer of the prostate involving the seminal vesicles." Microscopic examination of the specimen removed at operation verified the diagnosis. The patient, a 48 year old man, survived the operation for 5 months. Coffey also does not regard prostatic cancer as an indication for cystectomy. From the few reports of cases in which operation was performed on patients with prostatic cancer, it would seem that the cancer had grown from the prostate into the urinary bladder, and therefore that the condition had generally been diagnosed cancer of the bladder. This assumption applies, for example, to a patient operated on by Hellström, and also to the 8 patients Hinman (1939) was able to collect from the literature, and probably also to the 3 patients he operated upon himself. He is of the opinion that only cancer of the prostate involving the urinary bladder is an indication for this operation. Gutierrez (1949) recommends extirpation of the urinary bladder and the prostate only in the "advanced stage of carcinoma of the prostate involving the seminal vesicles, the lateral walls of the bladder, the trigone and one ureteral orifice," i.e., the operation should be done only in very advanced cases.

Millin performed retropubic extirpation of the bladder, seminal vesicles, and prostate in a 57 year old man for prostatic cancer with involvement of the bladder. However, the patient survived only 5 days. This radical type of operation he would recommend in: "cases where there is widespread involvement of the bladder base and in which an adequate removal would involve the ureteric orifice." For all other cases he recommends retropubic extirpation of the prostatic gland by the method he himself devised. He reported in 1947, 2 cases in which patients were successfully operated upon.

It is thus apparent that, except for Coffey's case, the method here proposed, with transplantation of the ureters and radical removal of the bladder, the seminal vesicles, and the prostate, has been used and recommended only for cancer of the prostate involving the urinary bladder. None of the workers in this field presents reasons why this operation should not be performed in the radical treatment of primary localized prostatic carcinoma.

In 1948 a 38 year old man was admitted to the hospital for treatment of an apparently localized prostatic cancer, and a radical operation was decided upon. The primary results were very satisfactory, and shortly afterward the same operation was performed on a 62 year old man. The case reports of these 2 patients follow.

CASE 1. J.4442/48. Male, aged 38 years. On December 5, 1948 total urinary retention occurred. Patient was admitted that day and 600 milliliters of urine was withdrawn. Rectal palpation revealed a well defined prostate, almost the size of a goose egg. The surface felt relatively smooth, the gland was firm, and, in some patches, hard. Apparently the rectal mucosa or neighboring tissues were not involved. Cancer of the prostate was assumed, and the diagnosis was verified later by electroresection. No evidence of metastasis was observed, and the general condition of the patient was good.

On December 28 the ureters were transplanted to the colon after the Coffey I method. After the wound had healed and urinary secretion became satisfactory, the bladder, prostate, and seminal vesicles were extirpated on January 11 by the method to be described in following pages. The operation presented no great difficulties. The tumor was easily enucleated from the pelvic wall and no metastases could be palpated in the pelvis. The prostate had been completely involved by a large typical cancer that was well demarcated and surrounded by a connective tissue capsule. Microscopic examination revealed scirrhous adenocarcinoma.

The postoperative course was very smooth and the temperature never exceeded 38 degrees C. After 8 days patient was able to sit up. He experienced no incontinence of the sphincter ani. He has had no inconvenience from the diversion of the urine, and since operation he has been able to lie all night without having to void urine. He returned to his work as storekeeper after 4 months, and has since felt well.

It is still too early to say anything definite about the prognosis in this case. As the patient is young and as the microscopic examination showed scirrhous adenocarcinoma, the danger of metastasis is, of course, great.[1]

[1]At re-examination 1½ years after the operation he felt well, no nocturnal frequency. No signs of metastasis.

CASE 2. J.4181/48. Male, aged 62 years. During the last few years patient had had symptoms typical of prostatic hypertrophy. On admission to the hospital on November 13, 1948 there was urinary retention. Rectal palpation revealed a somewhat enlarged, soft prostate with a fairly irregular surface. Hypertrophy was assumed, and on November 23 transvesical enucleation was performed. The operation was difficult because there was no defined adenoma to enucleate. It was necessary with the help of scissors to excise part of the prostate. Microscopic examination revealed adenocarcinoma scirrhosum.

As there was no evidence of metastasis, radical operation with extirpation of the bladder and of the prostate after previous transplantation of the ureters into the colon was decided upon. This transplantation was done on January 7, 1949 by the Coffey I method, and on February 1, the radical operation was performed by the same technique as used in Case 1. As the cancer had grown laterally through the prostatic capsule, enucleation was more difficult than in the previous case. The postoperative course was favorable. On examination 10 months later patient felt well and had had very little trouble from the diversion of the urine to the bowel. He has returned to his work as ship's engineer.

In these 2 cases then the primary operative results were very favorable. In neither patient did the operation have a deleterious effect on the general condition, and the postoperative course was smooth. Both have been cured and are very satisfied with the treatment, and both have returned to heavy manual labor. The reason this radical operation for localized prostatic cancer has hitherto not been performed is to be sought mainly in the high mortality attending extirpation of the bladder with transplantation of the ureters in cancer of the bladder. This mortality, however, has been reduced by simplified technique, controlled fluid balance, and sulfonamide and penicillin therapy. According to recent statistics, the operative mortality is now about 8 to 10 per cent (Hellström, Mayo Clinic, and others).

The operation is not much more extensive than many others for cancer. To make sure that a cancerous growth is radically removed it is often the practice today to remove the diseased organ completely, that is, to do a total gastrectomy, a pulmonectomy, or a duodenopancreatectomy. The present development in prostatic surgery is therefore in line with the advances made in other fields of surgery. It is probable that the operative risk of extirpation will prove less among patients operated on for prostatic cancer than among those operated on for cancer of the bladder, because the general condition of patients subjected to the former operation is not affected in the early stages, whereas the general condition of patients with cancer of the bladder is often poor as a result of prolonged hemorrhage and infection of the urinary tract.

Experience has shown that the risk of complications and of troublesome symptoms from the diversion of the urine to the colon is not great. Hellström recently re-examined 22 patients who had survived 1 to 5 years and says: "They have no serious intestinal troubles and are, considering their age, fit to work." Romanus has observed that disturbances in the sexual region are not essentially greater after this kind of radical operation than after ordinary extirpation of the prostate.

Prostatic cancer is no rare disease. As mentioned, 370 patients were treated during the last 10 years at the Sahlgren hospital, i.e. nearly 40 patients per year. As about 1400 patients with prostatic hypertrophy were treated during this period, the ratio between the frequency of cancer and hypertrophy of the prostate was about 1:4. The corresponding figures for the Caroline Hospital were 200 and 717, respectively. For purposes of comparison it might be mentioned that 480 men were treated for cancer of the stomach and 440 for cancer of the colon and rectum during the 10 year period. According to the literature (Giertz, Birdsal, and others) only 5 per cent of the cases of prostatic cancer are amenable to radical surgery, i.e. radical perineal prostatectomy. The combined radical operation, in which it is not necessary to spare the sphincter and in which a better survey of the small pelvis is possible, may increase the number of more advanced cases amenable to operation, and therefore I am inclined to think that a radical removal is possible in about 10 per cent or more of the patients admitted for prostatic cancer. Preoperative hormone therapy may render otherwise inoperable cases operable. Gutierrez, who is a warm advocate of perineal prostatectomy, even goes so far as to say: "As a preliminary treatment for

preparing the patient for radical perineal prostatectomy hormone therapy shows promise of increasing the percentage of operable cases from 10 to nearly 80 per cent."

In my opinion the most important factor in the radical treatment of prostatic cancer is that the disease be discovered before it becomes inoperable, that is that earlier diagnosis be made than has generally been the case hitherto. Unfortunately, prostatic cancer often gives no symptoms until it reaches an advanced stage. It is for this reason that so many patients do not seek aid before radical removal is impossible. It is therefore necessary to impress upon men over 40 the importance of seeking medical aid as soon as they notice the slightest trouble from the urinary tract. In the combat against intestinal cancer much is done to induce all people in cancer age to present themselves for regular examination. In my opinion, such regular examinations are just as important for prostatic cancer, because today it is possible to treat the disease just as radically as cancer of other organs, such as the stomach, for instance.

Examination for prostatic cancer is simpler than for intestinal cancer, and it is generally easier to establish a diagnosis. Rectal palpation is often sufficient to exclude the disease or to advise a more thorough examination. In cases in which rectal palpation leaves the examiner in doubt, the establishment of the diagnosis is more difficult: careful observation of the serum acid phosphatase index, urethrocystography, blood sedimentation rate, and cytologic examination of prostatic secretion may then be informative. The most important method is electroresection, which, if the finding is positive, establishes the diagnosis. On the other hand, a negative result will not exclude the condition. In the latter case, biopsy specimens may be obtained by perineal needle aspiration, or, if necessary, a biopsy specimen may be punched from the perineum. Before decision is made to do the major radical operation the diagnosis must be confirmed, because the operation is not without risk. Further, it is naturally necessary preoperatively to exclude the presence of remote metastases, which in some cases occur in a very early stage. Roentgen examination of the skeleton and the lungs is the most useful method for this purpose, but examination of the serum acid phosphatase may sometimes be informative. According to Giertz, the acid phosphatase is elevated in one-third of the patients with metastases as against one-tenth in those without metastases.

Young and middle aged men, of course, are most suitable for the combined radical operation but it may also be performed on men up to 65 to 70 years of age if their general condition, circulation, and renal function are good. It is preferable likewise that the cancer be localized in the prostate, although involvement of the bladder is of minor significance, since the latter is also removed. If the cancer has penetrated the capsule in other directions, operation is more difficult to perform, and the prospects of permanent cure are less favorable; even in such cases, however, the opportunity for close inspection of the operative field afforded by this method sometimes permits radical extirpation. If the tumor has overgrown the rectal wall, radical operation is not possible; injury to the rectal wall is a complication that can hardly be coped with in patients in whom the urine is diverted to the intestine.

In my opinion, the operation should be performed as a two stage procedure, the first stage being limited to the diversion of the urine. The second stage is, however, such a major operation that patients of advanced years are bad risks. It should be borne in mind also that prostatic cancer grows very slowly and that hormone therapy and castration may impede the progress of the growth and prolong survival a year or so. Hormone therapy, possibly in combination with castration, is therefore the treatment of choice for the aged patients or for those whose general condition is poor. If necessary, urination may be facilitated by electroresection.

TECHNIQUE

Two procedures are possible: suprapubic- and combined abdominoperineal extirpation. When operating on cancer of the bladder many surgeons prefer the suprapubic route (Coffey, Priestley, Ferris, Millin, and others) while others, probably the majority (Hinman,

Hellström, Smith, Strömbeck, Wilhelm and others) recommend the combined abdominoperineal method. Personally, I think the latter method is preferable in the treatment of prostatic cancer. It affords a better survey of the field of operation and thereby facilitates more radical removal, and besides it is also technically simpler. This fact applies especially to the laying bare of the rectum, which is often the most difficult and the most dangerous step, since injury to the rectal wall will jeopardize the success of the operation. To perform ureteral transplantation and extirpation in a one stage operation, as do Coffey and others, is, in my opinion, to increase the operative risk.

The case reports show that we performed the extirpation about 2 weeks or so after transplantation of the ureters. The extirpation was performed in the following manner:

After a suprapubic incision was made the urinary bladder was freed from the peritoneum, symphysis, and the lateral pelvic wall down to the prostate and the bottom of the pelvis. After the flow of blood had been arrested, the wound cavity examined, and the bottom of the pelvis palpated for any glands, the patient was placed in the lithotomy position. From a transverse incision in the perineum made a suitable distance from the rectum to avoid injury to the sphincter ani, the prostate and the seminal vesicles were enucleated as far as possible extracapsularly and separated from the rectum and the lateral pelvic wall by blunt dissection. The operation was simplified by the aid of an assistant who placed his hand through the incision and held the hand down in the pelvis and thereby rendered an exact orientation possible. After the urethra was divided a few centimeters distal to the prostate the puboprostatic ligament and the urogenital diaphragm were cut through. After the diseased organs were freed they were drawn up through the suprapubic incision. After the escape of blood had been checked, the field of operation was examined for metastases and sulfonamides and penicillin were sprinkled over the wounded surfaces. The suprapubic incision was then closed; the wound was drained by a couple of catheters left in the perineal incision.

ADVANTAGES

In my opinion *the greatest advantage of this combined operation over perineal extirpation* is that it permits a more radical operation than will perineal extirpation and also that a really radical operation is possible in the more advanced cases. Another advantage not to be forgotten is that the danger of urinary incontinence is eliminated. I think it justified, therefore, to recommend, in the radical treatment of prostatic cancer, extirpation of the urinary bladder, seminal vesicles, and prostate in preference to the perineal extirpation, at least in young and middle aged patients in good general condition.

SUMMARY

In Scandinavia perineal prostatectomy has been practically abandoned mainly on account of the high incidence of postoperative urinary incontinence and of recurrences. The patients are usually treated only palliatively with electroresection, hormone therapy, and castration. As the operative mortality after cystoprostatovesiculectomy for cancer of the bladder has now been reduced to 8 to 10 per cent, this operation is recommended for the surgical treatment of primary, localized, prostatic cancer. Two cases are reported in which this operation was performed abdominoperineally after transplantation of the ureters to the bowel. The operation caused no undue strain on the patients, and the primary results were very encouraging. Both felt well 12 months and 18 months, respectively, after operation. The operation is recommended as the method of choice in the treatment of localized cancer of the prostate in young and middle aged good risk patients. Patients of advanced age or patients in poor general condition should be treated with electroresection, hormone therapy, possibly in combination with castration.

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AUREOMYCIN IN THE PREPARATION OF THE INTESTINE FOR SURGERY

MUCH effort has been directed over the years toward finding an antibacterial agent which would remove all culturable bacteria from the intestinal tract of patients who are to undergo operation on this viscus. In our experience,[1, 2] aureomycin comes nearer to accomplishing this than any other agent studied so far.

When 750 milligrams of aureomycin were administered orally four times daily to 91 unselected hospitalized patients with various types of intestinal lesions requiring surgical measures, it was found that the culturable bacteria, except pseudomonas and proteus, were removed from the intestinal tract of 75 of these patients within a period of one and a fourth to six and a half days. In the remaining 16 cases Escherichia coli, Aerobacter aerogenes or Streptococcus fecalis persisted after the antibiotic had been administered from two and a half to five and a half days. In none of the 16 cases did clostridia remain. It was noted that within the recorded periods of study failure to remove the bacteria was related to the development of strains resistant to aureomycin or to factors which probably interfered with adequate contact between the antibiotic agent and the bacteria, as in cases of intestinal obstruction and perforated lesions of the intestine with associated abscess or fecal fistulas. It was observed that liquidity of the stools enhanced the removal of bacteria by means of aureomycin while constipation made it difficult or impossible to eliminate the culturable bacteria from the intestine. The administration of a saline laxative (phospho-soda) to liquefy the stools was adopted as a routine procedure in these studies with aureomycin.

Fecal specimens from patients who received aureomycin were assayed for this drug. Values for aureomycin ranged from 0 to 2,000 micrograms per gram of stool. Because of the instability of aureomycin the assays may have yielded figures that were too low. Values of 250 to 1,000 micrograms of aureomycin per gram of stool occurred commonly.

The only significant toxic symptoms from aureomycin consisted of nausea and vomiting. It was learned from experience that these symptoms could be kept to a minimum by feeding the patients when the aureomycin was administered. At times it was necessary to supply aluminum hydroxide with the drug to reduce nausea.

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Doses of either 500 or 250 milligrams of aureomycin given to 30 patients four times daily were not as reliable or as efficient as doses of 750 milligrams of the drug administered four times daily for intestinal antisepsis.

Twenty-two patients were given chloromycetin orally, 750 milligrams four times daily for two and a half to twelve days. It was possible to remove all culturable bacteria, except pseudomonas, in only 2 cases. In 20 cases Escherichia coli persisted in varying numbers; Streptococcus fecalis remained in 10 cases, and clostridia were culturable in 10 cases. By comparison, milligram per milligram, chloromycetin is not as effective or as reliable as aureomycin in removing culturable bacteria from the intestinal tract of man.

The administration of 500 milligrams of dihydrostreptomycin, orally, four times daily to 10 patients confirmed the general impression that this antibiotic agent may be temporarily effective as an antibacterial agent but that its value in intestinal antisepsis is greatly restricted by the rapidity with which resistant strains of micro-organisms develop.

The combination of 750 milligrams of aureomycin and 500 milligrams of dihydrostreptomycin was administered four times daily for from one and a half to five and a fourth days to 22 patients. The results indicated that there was little, if any, advantage in adding dihydrostreptomycin to aureomycin in the doses recorded.

Sulfasuxidine, in doses of 4 grams six times daily for one day and then in doses of 2 grams six times daily for subsequent days, was given orally in the preoperative preparation of patients with intestinal lesions. Thirty-five unselected patients were treated thus for one and a half to twenty-three days. In none of the 35 cases was it possible to remove all of the culturable bacteria. In only 4 of the 35 cases was it possible to eliminate temporarily all Escherichia coli. The number of Escherichia coli, however, tended to decrease from the third to sixth day after administration of the drug was started. Furthermore, Streptococcus fecalis increased in numbers as use of the drug was continued. In 21 of the 35 cases clostridia remained at the end of various experimental periods. Sulfasuxidine is far from being as efficient an antibacterial agent for intestinal antisepsis as aureomycin.

Sulfathalidine was administered to 10 patients in the same doses recorded for sulfasuxidine. The effectiveness of sulfathalidine was approximately comparable to that indicated for sulfasuxidine.

A comparative study of 194 cases of patients having various types of intestinal lesions which required surgical intervention indicated that aureomycin was by far the superior antibacterial agent. On the basis of these studies on preoperative intestinal antisepsis, it is recommended that aureomycin be given orally in doses of 750 milligrams four times daily for three or three and a half days.

WILLIAM H. DEARING.
FORDYCE R. HEILMAN.

UNIFORMITY IN REPORTING IMMEDIATE SURGICAL MORTALITY

IN discussions of various surgical procedures, especially radical operations for neoplastic disease, the factor of surgical mortality is significant. Offhand it would seem that surgeons might not differ in what is called immediate surgical mortality and yet in personal discussions and from reports in the literature it would appear that the definition of this term is not generally agreed upon. What is immediate surgical mortality? Death in the operating room? Death within

the first twenty-four, forty eight hours, one week or two weeks? Hospital mortality should be regarded as different from immediate surgical mortality since a patient may be operated upon and for some reason remain in the hospital for weeks or even months and then succumb because of some factor not immediately associated with the operation.

The writer would like to suggest in the interests of uniformity of expression throughout the literature and at surgical meetings that some agreement be reached by surgeons for the reporting of immediate surgical mortality. Further, he would like to suggest that a period of thirty days from the day of operation be more or less arbitrarily chosen as a period, if during which the patient succumbs, he be considered a surgical death regardless of what might be the cause of death. It is true, for example, that a fatal coronary occlusion, occurring two weeks after operation when the wound is healed and the patient already has been ambulatory, might have occurred even had the patient not undergone a major surgical operation. On the other hand, it might be argued that the strain of the operation induced or hastened the fatal accident. No definition is absolutely ironclad nor can one cover all possible contingencies. However, in the interests of uniformity throughout the literature it would seem highly desirable that a general agreement be reached by surgeons upon this question. There need be no formal pronouncement at principal meetings but the custom might become well established if in discussions and writings surgeons would begin to specify that immediate mortality in reference to a given operation was of a certain incidence and the statement added that immediate surgical mortality is arbitrarily defined as death within thirty days of the operation.

ALEXANDER BRUNSCHWIG.

HEMORRHAGE FROM THE UPPER GASTROINTESTINAL TRACT

THE control of hemorrhage is a basic problem in surgery. Control of loss of blood from wounds or ulcers on the external surfaces has always been accepted as a surgical problem. Even in the case of concealed hemorrhage in soft tissues or into the peritoneal or thoracic cavities there has been unanimous agreement that management should be surgical. The treatment of choice in the control of serious bleeding which may endanger life—the prompt ligation of the bleeding vessel—is obvious.

In the case of hemorrhage from the upper gastrointestinal tract there is sometimes confusion as to whether one ought to treat the peptic ulcer which most commonly causes such bleeding or to control the hemorrhage. A decision on this point is simple in cases in which the bleeding has been of the rate or amount to cause easily observable evidences of great blood loss. The fact that minimal hemorrhage from smaller vessels, whether in the upper gastrointestinal tract or on the surface, are self-controlled by clotting, by retraction or constriction of vessels, or both, is well understood. In surface wounds, cessation of such bleeding is apparent. In bleeding from the upper gastrointestinal tract cessation of bleeding is less easily discernible, and the amount of blood loss less easily evaluated by visible means. The amount of blood which the patient vomits does not accurately indicate the amount of blood lost since it is usually mixed with stomach content, the stomach does not empty completely and blood may pass down the gastrointestinal tract.

It is a well known surgical concept, fully corroborated by experiences in World War II, that a normal healthy person tolerates acute

blood loss better than blood loss continuing over a long period of time or frequent intermittent losses of blood. Significantly Stewart has shown that the amount of blood lost from patients with massive hemorrhage from the upper gastrointestinal tract as measured by blood volume studies and red cell mass, does not indicate the amount of blood necessary for replacement. This deficit is quite likely due to the blood loss from the tissues as well as from the blood stream and it is necessary to replace blood not only in the major vessels but in the smaller ones and in the tissues as well. The more serious and prolonged the hemorrhage, the more difficult becomes the problem of adequate replacement.

Blood lost from vessels of sufficient size to exsanguinate the patient requires prompt ligation whether from an easily observable lesion or from the gastrointestinal tract where the amount and rate of blood loss must be determined by inferential means. While direct measurement of blood loss from a bleeding duodenal or gastric ulcer is not accurately possible, some approximation can be made. Bleeding duodenal ulcers commonly pour most of the blood lost into the stomach. Occasionally no blood will be found in the stomach but in most cases a fair index of blood loss can be had by continuous gentle aspiration of the stomach.

Clots obviously cannot be aspirated through a Levin tube, however fresh blood diluted with gastric juice is removed without difficulty. In the evaluation of the problem of the patient with bleeding from the upper gastrointestinal tract, determination of whether the patient has stopped bleeding is more important than estimation of the amount of blood lost. If bleeding has stopped, blood replacement will be effective. If massive bleeding continues, blood transfusions will be only temporarily effective, if at all.

Any aid in stopping hemorrhage from the upper gastrointestinal tract is of advantage, even though bleeding is not sufficient to endanger life. Thrombin is effective if the bleeding is not too massive and if it can be applied directly to the bleeding point. In the stomach, acid must be neutralized if thrombin is to maintain activity. Buffer solution can neutralize the acid of the stomach for sufficient time to permit thrombin to act effectively. If bleeding is so active as to prevent thrombin reaching the bleeding point or if it is prevented from reaching the area because of a crater partially filled with clot, thrombin cannot be expected to stop the bleeding. Whatever the result, the use of thrombin and buffer with a tube in the stomach does give all important information as to whether bleeding has stopped. If fine clots only are found in the aspirate one can be relatively sure bleeding has stopped; if bright red blood continues to be aspirated other means ought to be employed to stop the bleeding.

The most common cause of bleeding from the upper gastrointestinal tract is peptic ulcer, and the majority of these are duodenal. Bleeding from carcinomas, esophageal varices or gastritis are, while not so frequent as peptic ulcer, equally troublesome. Every effort ought to be made to reach an accurate diagnosis although this is not so important immediately as the control of the hemorrhage. In cases in which the bleeding has stopped, diagnostic procedures can be carried out later. However, in cases in which it is important to determine the cause or site of bleeding, barium may be given by mouth and sometimes is of help. Carcinomas or large ulcers may at times be outlined by this procedure. Such procedure should not delay active measures to bring the bleeding under control.

Most troublesome, until recently, has been the differentiation between bleeding from

esophageal varices and lesions lower down. The introduction of an effective and simple tampon by Patton, and later by Blakemore, has changed this problem markedly. Not only is it possible to stop bleeding from esophageal varices by this method and to maintain hemostasis for a sufficient time to plan and execute definitive therapy, but it is also possible to determine definitely whether the bleeding has stopped.

Recent advances have been made in the treatment of bleeding from the upper gastrointestinal tract. These have not been spectacular but have come about through a more realistic approach to the problem. The old concept that all patients with bleeding from the upper gastrointestinal tract be put to bed, given heavy and frequent doses of morphine, ought no longer be tolerated. Brown and Meyers reported a mortality of 87 per cent in cases of massive hemorrhage from peptic ulcer treated medically as compared to 12.5 per cent in cases treated surgically at the Detroit Receiving Hospital. The majority of patients bleeding from the upper gastrointestinal tract do not rapidly become exsanguinated, but continuous or repeated smaller losses of blood may be just as lethal as more massive hemorrhage, if not properly controlled. All such patients should have careful evaluation not only regarding the lesion causing the bleeding and the amount of blood lost, but also should have prompt therapy. In cases of massive bleeding the hemorrhage must be stopped promptly. Undue delay decreases the patient's chances of survival. Whether the bleeding is stopped by thrombin and buffer, by tamponade, by ligation of the bleeding vessel, or by gastric resection is not so important as is the effective control of the hemorrhage. Such an aggressive approach to the problem of massive upper gastrointestinal hemorrhage is rewarded by the salvage of a much greater percentage of these patients. CHARLES G. JOHNSTON.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

THE fifth edition of Christopher's *Textbook of Surgery*[1], written by 198 distinguished American authors, is again a "concise presentation of surgery, with maximum authority." These authors have presented their material with emphasis on acceptable and noncontroversial principles of modern world wide surgery. Several changes in organization from the previous edition have been made, including grouping the various sections on the motor skeletal system in consecutive order. All divisions have been extensively revised, and 31 new sections have been added. The new chapters on chemotherapy of surgical infections, the esophagus, and preoperative and postoperative care are among the latter.

The subject matter ably covers the field of general surgery from important basic principles to specific treatment, and all material is current. The 1,465 illustrations are done in a clear, practical manner, and the physical form and composition of the text are excellent, making all material quickly available for reference. It is believed that this fifth edition of what has become a widely used standard textbook of surgery is a timely and valuable contribution.

LAWRENCE CHAFFIN.

THE third edition of *Cystoscopy and Urography*[2] by James B. Macalpine has been revised and greatly enlarged. It consists of 554 pages, 338 illustrations, and 15 colored plates. The book carries a very good index.

The author has included an excellent discussion of the mechanics and physics of cystoscopic instruments. He has combined urological instrumentation with much anatomy, physiology, pathology, and bacteriology.

Many workers would not agree with the author in not investigating the urinary tract after acute infections of the tract, and most modern urologists would disagree with the author's nomenclature in the classification of bladder tumors. He speaks of the benign papilloma although doubtful whether there is such an entity. The illustrations of this section are excellent.

Some space is given to a discussion of transurethral prostatic resection. It is believed that the omission of hemolysis and lower nephron nephrosis is noteworthy.

The section on urography is very complete. The dangers of intravenous urography could be emphasized more definitely.

All in all, this is an excellent book and should be in the library of all urologists and cystoscopists. One has the feeling after finishing the book that a complete kaleidoscopic picture of the entire field of urology has been painted very well.

WILLIAM J. BAKER.

A FIELD much wider than the title indicates is covered in *An Atlas of Amputations*[3] by Donald B. Slocum. The theme of the book is directed toward the maximum rehabilitation of the individual with an amputation.

The author divides the material into four parts. In the first, he discusses some general principles and also the specific indications for amputation including trauma, infection, thermal injuries, peripheral vascular diseases, and congenital anomalies.

In part 2 Dr. Slocum describes the physiologic response of the skin, muscles, tendons, fascia, nerves, periosteum, bones, cartilage, synovia, and blood vessels to proper care. Difficulties encountered in improper care are mentioned and the indications for skin grafts in amputations are discussed.

The positioning and draping of the patient are illustrated and described, and supplies necessary in various procedures are listed.

A separate chapter on anesthesia as applied to amputations was written by E. M. Papper.

Part 3 contains in detail the surgical techniques in open and closed amputations at all levels in both upper and lower extremities. This part is profusely illustrated, each procedure is evaluated and discussed in separate paragraphs, as to the skin incision, development of flaps, section of soft tissues, bone section, care of vessels and nerves, closure, and postoperative care.

Part 4 covers the convalescent period beginning from the closure of the surgical wound to the completion of the rehabilitation.

Stump hygiene is outlined and complications of the final amputation stump are discussed in detail. An excellent discussion of pain is included. A chapter on the mechanics of normal and amputee gait is pictorially presented and all aspects of prostheses making and fitting are well covered.

Dr. Donald L. Rose superbly presents the use of physical medicine in the treatment of lower ex-

[1] A TEXTBOOK OF SURGERY BY AMERICAN AUTHORS. Edited by Frederick Christopher, B.S., M.D., F.A.C.S. 5th ed. Philadelphia: W. B. Saunders Co., 1949.

[2] CYSTOSCOPY AND UROGRAPHY. By James B. Macalpine, D.Sc. (Honoris Causa), F.R.C.S. (Eng.). 3d rev. enl. ed. Baltimore: The Williams & Wilkins Co., 1949.

[3] AN ATLAS OF AMPUTATIONS. By Donald B. Slocum, M.D., M.S. St. Louis: The C. V. Mosby Co., 1949.

tremity amputations, and special chapters are devoted to rehabilitation of the upper extremity amputee and the amputee in sports.

The material in the book is complete, readily available, interestingly written, and well edited. The illustrations are well chosen and placed. This is an excellent book for anyone desiring to know the best about amputations. E. J. CUMMINS, JR.

A SHORT textbook which has been written mainly for students, Colby's *Essential Urology*[1] is based upon urology as it is taught at the Massachusetts General Hospital.

Modern urology has developed to the point where the better textbooks to be complete must contain such a volume of information that they are encyclopedic in their scope. Since they are written primarily for the specialist in urology, many of the simpler facts and principles which the beginner needs for a proper understanding of the subject are not included. Hence the medical student, when he consults such a treatise in the limited time which the curriculum permits, finds himself confronted with a maze of conflicting information, and he fails to achieve a proper understanding of the fundamental principles of the subject. Instructors in urology have long felt the need of a short, well planned textbook which has been written from the medical student's point of view.

Of the few such books which have recently appeared, Colby's *Essential Urology* is undoubtedly one of the best. This short volume of 580 pages is remarkably well written in a direct and easily readable style. It is divided into 3 sections, the first of which is devoted to anatomy, embryology, and physiology, the second to methods of examination, and the third to diseases of the genitourinary organs.

In spite of its brevity this book contains a surprising amount of information. The author stresses fundamental principles and presents only accepted facts in an unbiased manner. In the section on diseases of the genitourinary organs gross and microscopic pathology is emphasized.

This excellent volume shows the results of scholarship and long clinical experience. It is printed with easily readable type on gloss paper of good quality. The illustrations are excellent. Although it is intended primarily for medical students it may be read with profit by urologists as well.

FREDERICK A. LLOYD.

THE present volume *The Eye and Its Diseases*[2] represents the second edition of a standard American textbook of ophthalmology, the first edition of which appeared in 1936. This edition adheres to the outline and contents of the first edition so far as it is possible; additional chapters have been added on illumination, physiologic chemistry, and gonioscopy. Recent advances have been carefully considered, particularly concerning therapeutics and the ophthalmic uses of the antibiotics. The chapter bibliographies should prove very valuable in that they give the best recent references available on the particular subject. The general format is definitely improved, with a larger double column page which makes for better and easier reading.

This book has two characteristics that both add to and detract from its value. The first is that the book is written by 92 different contributors. Although this means that each chapter is written by an authority on the subject, some lack of uniformity in presentation of the material results. It also means that there is some unavoidable repetition with occasional difference of opinion in the various chapters. The second characteristic is that this is a discussion of the eye in all its phases, as suggested by the title, rather than merely a textbook of diseases of the eye. Therefore, in a relatively short textbook, there are included many subjects in the related fields of ophthalmology such as light and lighting, hygiene of the eye, and medical jurisprudence. This results in less space devoted to some of the more important eye diseases. Also, many limited conditions are given separate chapter headings by an individual author rather than being included in the appropriate general chapter.

The broad scope of the material covering all of the fields related to the eye and the manner in which it is presented make this a very valuable textbook for the student of ophthalmology and for the practitioner in related fields of medicine. To the advanced student of ophthalmology it will not have the appeal of some of the more detailed references. However, this new edition is a very definite addition to any collection of books on ophthalmology.

T. E. SANDERS.

THE physician relies more and more on the clinical laboratory as an aid in diagnosis. The book *Clinical Pathology; Application and Interpretation*[3] fills a need for a clear, precise discussion of the interpretation and application of laboratory findings. The author begins with a clinical situation and discusses the applicable laboratory procedures which should be selected and their contribution to the problem. He gives the technical and physiologic limitations of the procedures without giving the technique. The method of collecting and handling of specimens to be sent to the laboratory is given, because the correct type of specimen is very important in obtaining dependable results.

The book is divided into 9 chapters, dealing with infectious diseases, diseases of the gastrointestinal system, diseases of the respiratory system, diseases of the kidney and urinary tract, diseases of the blood, diseases of the cardiovascular system, and metabolic

[1] ESSENTIAL UROLOGY. By Fletcher H. Colby, M.D. Baltimore: The Williams & Wilkins Co., 1950.

[2] THE EYE AND ITS DISEASES. Edited by Conrad Berens, M.D., F.A.C.S., and 92 international authorities. 2d ed. Philadelphia and London: W. B. Saunders Co., 1949.

[3] CLINICAL PATHOLOGY; APPLICATION AND INTERPRETATION. By Benjamin B. Wells, M.D., Ph.D. Philadelphia and London: W. B. Saunders Co., 1950.

and endocrine disorders. The eighth chapter, which deals with clinical laboratory studies in surgery, will be of special interest to surgeons. It contains a discussion of dehydration, bleeding tendencies, blood transfusions, and intestinal obstruction. The ninth chapter is on clinical laboratory studies in obstetrics, including normal pregnancy, sterility, toxemia of pregnancy, the Rh factor, and anemia of pregnancy. With the assistance of Dr. A. E. Moon, the author has added an appendix on laboratory aids in symptom diagnosis, tests used in the study of jaundice and liver disease, normal values and findings in disease for sputum, cerebrospinal fluid, and blood chemistry.

This book is not intended to be a text in medicine or a laboratory manual. It consists of 390 pages, 38 tables, and 32 figures. The material is well chosen and should be of great assistance to the general practitioner, the specialist, the clinical pathologist, and to medical students. OPAL E. HEPLER.

THE comprehensive 200 page, beautifully illustrated monograph, *Úlceras de las extremidades inferiores de origen vascular*[1], is devoted principally to the ulcers of the lower extremity of venous origin.

The author points out that when injury, whether of traumatic or infectious origin, occurs in the lower extremity, there are initiated, as elsewhere, certain reparative processes. He also concludes that complete repair is frustrated in two circumstances: (1) when a sufficiently severe injury occurs on a physiologically normal extremity; (2) when injury of a lesser degree occurs on an extremity the seat of previous physiological disturbance. In either case, when the insult overcomes the existing reparative power of the extremity we have conditions favorable for the appearance of an ulcer, and with this a further barrier to subsequent normal repair.

The principal "tropho-regulators" of the lower extremity are vascular, i.e. arterial, venous, and nervous. The lymphatic factor is of less importance and its changes appear secondary to the other mechanisms.

The normal trophism of the extremity is largely dependent upon circulatory conditions. An adequate supply of arterial blood is essential, and if this is deficient there is produced ischemia with anoxia, which has severe trophic repercussions, leading eventually to a necrosis of tissue. Adequate venous drainage is also indispensable, and if this is impeded stasis is produced with asphyxia.

The margin of tolerance from ischemia is much less than that from stasis; the alterations from anoxia are quickly irreversible; the alterations from asphyxia are tolerated for a far longer period.

The three accepted causes of chronic venous insufficiency are discussed with thoroughness and all of the principal recent work along this line is carefully noted: (1) the obstruction of the deep veins consequent to thrombophlebitis, more rarely due to neoplastic invasion or external compression; (2) deep, venous, valvular insufficiency following a thrombosis which has become canalized; (3) primary, hereditary, valvular insufficiency without antecedent thrombophlebitis.

Treatment, the author directs toward cure of the ulcer and prevention of recurrence. The ulcer is relatively easy to cure, but recurrence is almost constant, if the initial circulatory deficiency is not corrected.

Conservative treatment includes bed rest, elevation, compression bandaging with the paste-boot or elastic bandage, and treatment of the factor of infection, along with consideration of diet and health in general. Radical treatment is usually necessary in the severe cases, following as much improvement as possible by conservative measures. The author prefers excision followed by immediate skin grafting. Preparation, in addition to the conservative measures listed, includes: ruling out the existence of syphilis, diabetes or other illness; determination of hemoglobin, red blood count, coagulation time and serum protein; a diet rich in vitamins (especially A and C); an interdiction of alcohol and tobacco.

Several requirements are listed which must be met in assuring a satisfactory take of the graft: rigorous hemostasis; the use of none but nonabsorbable suture material; careful elimination of any necrotic or devitalized tissue in the graft sites, such as that from the application of clamps or from cautery excision; and finally an adequate pressure bandage. A thin split graft is the type nearly always recommended. The methods of treatment of the venous insufficiency are described at length, and a brief review such as this cannot do the work justice.

A wealth of material is presented. A comprehensive bibliography is attached. It is unfortunate that this monograph is not translated in English.

NEAL OWENS.

IN the third edition of Wesson's *Urologic Roentgenology*[2] the text has been modernized and condensed, and old illustrations have been replaced with new so that practically all urologic conditions are depicted. This makes it an excellent book for a review of the characteristic films for the roentgenologic or urologic resident.

The emphasis is upon x-ray interpretation rather than technique, but the text contains many helpful hints and "shall nots" which should be of interest to students of either specialty.

The illustrations of roentgenograms are excellently reproduced. The bibliography is brief, and appears at the end of each chapter, but does contain references to the recent literature, some of which are included because of their extensive bibliographies.

All radiologists will probably flinch at the author's conception of storing films, that is to trim all excess

[1] ÚLCERAS DE LAS EXTREMIDADES INFERIORES DE ORIGEN VASCULAR; PONENCIA DEL PRIMER CONGRESO DE LA ASOCIACIÓN ESPAÑOLA DE CIUJANOS BARCELONA, NOVIEMBRE DE 1949. By P. Piulachs. Barcelona: Salvat, 1949.

[2] UROLOGIC ROENTGENOLOGY. By Miley B. Wesson, M.D. 3d rev. ed. Philadelphia: Lea & Febiger, 1950.

film away and place the remainder in the patient's chart with tape. However, the majority of the author's concepts regarding the role of roentgenograms and roentgenoscopy are perfectly valid, and there are many admonitions as to the safe use of the ionizing x-ray beam.

In brief, the book is a small complete descriptive atlas of urologic diseases as seen in the eyes of the film viewer. There is some discussion of the many techniques involved. The author uses numerous short histories which are very interesting because many of them are representations of early mistaken diagnoses.

The book is highly recommended, particularly to the resident and young specialist group.

F. H. SQUIRE.

IN the fourth edition of his compact 268 page handy reference size volume the author of *Practical Neurological Diagnosis*[1] once more accomplishes his objective "to present a simple account of the principles of neurological diagnosis . . . for students and practitioners." As in previous editions the material is presented in a systematic and comprehensive manner, correlating anatomy and physiology with neurological signs and symptoms and outlining a practical approach to the neurological examination. This is admirably achieved by emphasis upon the localization of lesions and their basic pathologic physiology.

Notable changes from the third edition include the addition of a section on the hypothalmus and a glossary of commonly used terms, complete revision of the chapter on the cerebellum, and a general rearrangement of material. Relatively unchanged are the excellent chapters on the cerebrospinal fluid and on roentgenologic diagnosis. The former includes a concise synopsis of the important anatomy and physiology, a description of the technique of lumbar puncture, and several clear, handy charts and diagrams summarizing the principal pathologic changes found in the cerebrospinal fluid in the common neurological diseases. The chapter on x-ray diagnosis consists of a description of the roentgenologic procedures commonly used in the diagnosis of diseases of the central nervous system and an excellent impartial discussion of the values and limitations of each. Still regrettably absent from the book, however, is any section on lesions involving the peripheral nerves.

This book is of special value as a handy reference volume for the practitioner with a modest training in neurology to whom neurological problems present an unusual and difficult challenge in diagnosis. Students too will find its simple, systematic approach extremely helpful in organizing their thinking regarding problems in neurology, as well as a valuable guide to developing technique in neurological examination.

HALE HAVEN.

[1]PRACTICAL NEUROLOGICAL DIAGNOSIS; WITH SPECIAL REFERENCE TO THE PROBLEMS OF NEUROSURGERY. By R. Glen Spurling, M.D. 4th ed. Springfield, Ill.: Charles C Thomas, 1950.

AN excellent textbook for students and a handy reference for the practitioner *Mitchell-Nelson Textbook of Pediatrics*[2] continues to hold its deserved position. The fifth edition has been completely revised and brought up to date with many new additions. Detailed discussions about technical subjects have necessarily been limited to the minimum but sufficient references are given to direct the reader to the desired information. As in all fields of medicine the expanse of knowledge has grown so rapidly that it is almost impossible to condense the material on pediatrics into one volume.

The chapter on physical growth and development answers numerous common simple questions frequently asked by parents. It is refreshing to have the old myths of tongue tie and thymus depreciated and to hear the expression of good common sense opinions about such things as circumcision and allowing baby to sleep on its stomach. This chapter should be a welcome review for the practitioner and a store of practical knowledge for the neophyte pediatrician. A review of the chapter on genetic and congenital deformities would be very helpful to any physician who has the task of advising parenthood to parents of a congenitally defective child. The usual groupings of systems are adequately covered and brought up to date. A very valuable reference section is the appendix of normal values with explanation of methods of conversions and calculations.

L. MARTIN HARDY.

THE volume *Menstruation and Its Disorders*[3] presents the information and attendant discussion of the annual conference of the National Committee on Maternal Health and is a superior résumé of the latest and most pertinent facts of menstruation. The scientific aspects are well covered by discussions of alkaline phosphatase, lipase, chemical histology, and histophysiology of the endometrium. The physiology and pharmacology of the myometrium are also included. Enzymes in the ovarian tissue of the experimental animal are discussed.

The understanding of menstruation is further enhanced by an excellent description of the blood flow in the endometrial vessels and its relation to edema, buckling of the coiled arteries, stasis, necrosis, and finally bleeding. The control of the peripheral vascular system by depressor and excitor factors is recounted and correlated with the problems of blood flow within the endometrium.

The experimental work and the clinical significance of the menstrual toxin are completely elaborated and summarized.

From a clinical standpoint there is a beautiful presentation by Hertig and Rock of abortive human ova and associated endometria which is very en-

[2]MITCHELL-NELSON TEXTBOOK OF PEDIATRICS. Edited by Waldo E. Nelson, M.D. 5th ed. Philadelphia and London: W. B. Saunders Co., 1950.

[3]MENSTRUATION AND ITS DISORDERS; PROCEEDINGS OF THE CONFERENCE HELD UNDER THE AUSPICES OF THE NATIONAL COMMITTEE ON MATERNAL HEALTH. Edited by Earl T. Engle. Springfield, Ill.: Charles C Thomas, 1950.

lightening on the subject of the etiology and pathogenesis of spontaneous abortion. The facts presented should be known to all.

The atypical secretory phase of the endometrium is shown and a critical review of basal body temperature curves is made. Functional uterine bleeding and the histologic changes in the endometrium are discussed from both a clinical and pathological viewpoint. Knowledge of this subject as presented will lead to the improved treatment of patients.

This book has interest for and supplies recent information to both the clinician and investigator. Stimulating thoughts and ideas abound.

JOHN I. BREWER.

BOOKS RECEIVED.

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

DIAGNOSIS AND TREATMENT OF TUMORS OF THE HEAD AND NECK; (NOT INCLUDING THE CENTRAL NERVOUS SYSTEM). By Grant E. Ward, M.D., D.Sc., F.A.C.S., and James W. Hendrick, M.D., M.S. Baltimore: The Williams and Wilkins Co., 1950.

PYE'S SURGICAL HANDICRAFT; A MANUAL OF SURGICAL MANIPULATIONS, MINOR SURGERY, AND OTHER MATTERS CONNECTED WITH THE WORK OF SURGICAL DRESSERS, HOUSE SURGEONS AND PRACTITIONERS. Edited by Hamilton Bailey, F.R.C.S.(Eng.). 16th rev. ed. Baltimore: The Williams and Wilkins Co., 1950.

CRANIOPLASTY. By David L. Reeves, A.B., M.D. Springfield, Ill.: Charles C Thomas, 1950.

BONE AND JOINT DISEASES; PATHOLOGY CORRELATED WITH ROENTGENOLOGICAL AND CLINICAL FEATURES. By J. Vernon Luck, M.D., M.S. (Ortho), F.A.C.S., F.I.C.S. Springfield, Ill.: Charles C Thomas, 1950.

SURGICAL NURSING. By Eldridge L. Eliason, A.B., M.D., Sc.D., L. Kraseer Ferguson, A.B., M.D., and Lillian A. Sholtis, R.N., B.S., M.S. 9th rev. ed. Philadelphia, London, Montreal: J. B. Lippincott Co., 1950.

TO PROSPECTIVE MOTHERS. By William E. Hunter, M.D., F.A.C.S., and Bernard H. Smith, B.A., M.D. Boston: Bruce Humphries, Inc., 1950.

THE BREAST STRUCTURE: FUNCTION: DISEASE. Edited by F. D. Sander, M.B., B.Ch. (Camb.), F.R.C.S. (Eng.). Baltimore: The Williams & Wilkins Co., 1950.

THE ESOPHAGUS AND PHARYNX IN ACTION; A STUDY OF STRUCTURE IN RELATION TO FUNCTION. By William Lerche, M.D. Springfield, Ill.: Charles C Thomas, 1950.

NOUVELLE PRATIQUE CHIRURGICALE ILLUSTRÉE. By Jean Quénu. Paris: G. Doin & Cie, 1950.

ANATOMIE CLINIQUE ET OPÉRATOIRE. By J. Maisonnet and R. Coudane. Vols. 1, 2, 3. Paris: G. Doin & Cie, 1950.

THE PHYSIOLOGICAL BASIS FOR OXYGEN THERAPY. By Julius H. Comroe, Jr., and Robert D. Dripps. Springfield, Ill.: Charles C Thomas, 1950.

CEREBRAL PALSY. By John F. Pohl, M.D. St. Paul: Bruce Publishing Co., 1950.

NUTRITION IN HEALTH AND DISEASE. By Lenna F. Cooper, B.S., M.A., M.H.E., Sc.D., Edith M. Barber, B.S., M.S., Helen S. Mitchell, A.B., Ph.D., and Henderika J. Rynbergen, B.S., M.S. 11th rev. ed. Philadelphia, London, Montreal: J. B. Lippincott Co., 1950.

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CEREBRAL ANGIOGRAPHY. By P. Almedia Lima. Introduction by Egas Moniz and foreword by Sir Hugh Cairns, K.B.E., D.M., F.R.C.S. London, New York, Toronto: Geoffrey Cumberlege Oxford University Press, 1950.

THE MANAGEMENT OF OBSTETRIC DIFFICULTIES. By P. Titus, M.D. 4th ed. St. Louis: C. V. Mosby Co., 1950.

LES FROTTIS VAGINAUX ET CERVICAUX; BASES BIOLOGIQUES ET INDICATIONS CLINIQUES GYNÉCOLOGIQUES. By J. Paul Pundel. Liège: Éditions Desoer; Paris: Masson & Cie, 1950.

THORACIC SURGERY. By Richard H. Sweet, M.D. Philadelphia, London: W. B. Saunders Co., 1950.

PATHOLOGIC PHYSIOLOGY; MECHANISMS OF DISEASE. Edited by William A. Sodeman, M.D., F.A.C.P. Philadelphia, London: W. B. Saunders Co., 1950.

AN ATLAS OF HUMAN ANATOMY. By Barry J. Anson, Ph.D. Philadelphia, London: W. B. Saunders Co., 1950.

EVALUATION OF INDUSTRIAL DISABILITY. Prepared by the Committee for Standardization of Joint Measurements in Industrial Injury Cases of the California Medical Association and Industrial Accident Commission, State of California. New York: Oxford University Press, 1950.

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